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NAME OF AUTHOR: PAULA CORABIAN

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DIRECT COSTS OF HEALTH CARE FOR DIABETES WITH COMPLICATIONS: SASKATCHEWAN, 1991

BY

PAULA CORABIAN

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THE UNDERSIGNED CERTIFY THAT THEY HAVE READ, AND RECOMMEND TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH FOR ACCEPTANCE, A THESIS ENTITLED **'DIRECT COSTS OF HEALTH CARE FOR DIABETES WITH COMPLICATIONS: SASKATCHEWAN, 1991'** SUBMITTED BY **PAULA CORABIAN** IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF PUBLIC HEALTH IN HEALTH POLICY RESEARCH.

Dedication

I would like to dedicate this thesis to my husband **Mihai Ovidiu Corabian** and my daughters **Ioana and Gabriela Corabian**, who have encouraged me and supported me in my academic endeavors.

Abstract

Previous estimates of diabetes cost in Canada have been limited to aggregate costs from various and disparate sources and may not be translated into patient-level cost inputs for planning resource use and predicting possible savings due to prevention of complications.

The objective of this study was to estimate patient-level cost of care according to complicating conditions and important cost drivers among persons with diabetes in Saskatchewan in 1991.

Costs were estimated using data from Saskatchewan's health services databases. Multivariate regression was used to determine the impact of clinical and demographic variables on individual costs.

Our estimates indicated a large inter-individual variation in cost. Patients with no complications had the lowest cost and those with renal, neurological and cardiovascular complications had the highest costs. Regression results indicated a positive association between demographic variables and costs. All disease severity variables were positively associated with costs and of the expected order of magnitude.

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Abbreviations

Assoc. – association

C – cardiovascular complications are present

CHD – coronary heart disease

CHF – congestive heart failure

CO – cardiovascular and ophthalmic complications are present

CVD – cardiovascular disease

DM – diabetes mellitus

ER – emergency department

ESRD – end-stage-renal-disease

FFS – fee-for-service benefit plan

HbA_{1c} – glycosylated hemoglobin

HMO – health maintenance organization

IDDM – insulin-dependent diabetes mellitus

IHD – ischemic heart disease

LOS - length of stay in hospital

MI – myocardial infarction

N – neurologic complications are present

N/A – information is not available

NC – neurologic and cardiovascular complications are present

NCO – neurologic, cardiovascular and ophthalmic complications are present

NIDDM – non-insulin dependent diabetes mellitus

NO – neurologic and ophthalmic complications are present

NoComp – none of the complications mentioned above are present

NS – not statistically significant

O – ophthalmic complications are present

OLS – ordinary least squares

PVD – peripheral vascular disease

R – renal complications are present

RC – renal and cardiovascular complications are present

RCO – renal, cardiovascular and ophthalmic complications are present

RN – renal and neurologic complications are present

RNC – renal, neurologic and cardiovascular complications are present

RNCO – renal, neurologic, cardiovascular and ophthalmic complications are present

RNO – renal, neurologic and ophthalmic complications are present

RO – renal and ophthalmic complications are present

Sign. – significance level

SS – statistically significant

USA – United States of America

ys – year(s)

1. Introduction

Diabetes mellitus is a chronic and potentially disabling disease, which represents a major public health and clinical concern [20, 56]. Currently, it has been estimated that diabetes affects 120-140 million people worldwide [3, 102] and more than 1 million people in Canada [28]. There appears to be a trend toward increased diabetes prevalence and incidence as the population ages and improvement in diabetes care and management increases the survival of people after diagnosis [3, 20, 56, 28, 102].

Diabetes requires careful and continuous monitoring, medical management and self-care and has long-term major implications, not only for the health and well being of the affected people but also for the costs to the patients, their families and society as a whole. Considerable costs are associated with diabetes in terms of complications and related disabilities, patient quality of life. and health care system resources, which result in a significant clinical and economic burden being attributable to the disease.

There are emerging therapies designed to offer an alternative to the existing standard therapies, which may improve diabetes control and help reduce the incidence of some complications and co-morbidities. To assess the role of these new therapies and perform accurate economic evaluations, it is necessary to have recent and comprehensive data on the economic implications of the relevant diabetes-associated complications. However, accurate data are scarce and the existing comprehensive cost estimates are provided on an aggregate level that may not be readily translated into inputs necessary for an economic model.

Information concerning the influence of various demographic and clinical factors on health services utilization and costs for diabetes care is also needed. Some of the most recently published studies using patient-level cost data have attempted to identify health care cost drivers by using predictive modeling approaches. However, most of these studies are specific to the managed care experience in the United States and the utility of their findings for accurately predicting health care costs in other cohorts is limited. None of these studies has been conducted in Canada.

With these in mind, we designed a retrospective observational study of health care costs for a cohort of patients with diabetes in Saskatchewan, Canada, in the calendar year 1991. We have obtained data from the Saskatchewan Health in order to analyze the costs of registered Indian and general populations with diabetes. The main objective of this study was to calculate patient-level cost estimates for the health care of patients with diabetes, according to the presence or absence of specific diabetes-associated complications. Total annual costs

of health care per case were measured. Using a regression equation, the determinants of costs, including complicating conditions, were estimated.

These data employed will allow us to compare persons by age, gender, and race (i.e., registered Indian population versus non-registered Indian population). It also makes provision for identifying the costs of additional, related services of specific diabetes-associated complications. The investigation will provide essential information for health care decision makers to manage diabetes in Canada. The results may be useful for identifying both patients at a higher risk for hospitalization and possible interventions for diabetes management programs. It will also help forecast the future costs of diabetes.

2. Background

Current topics of interest to health care planners, providers, and payers, among others, are the recognition of the clinical and economic burdens of diabetes and the realization that they may be growing [2, 39, 62, 65, 96]. These topics have stimulated interest in reducing the incidence of diabetes and its associated complications. Recent evidence has suggested that more intensive diabetes control may be cost-effective since it results in improved glycemic control, which in turn leads to fewer complications [4, 17, 25, 26, 27, 32, 36, 98, 99, 100]. Emerging therapies offer an alternative to standard regimens (insulin and/or oral antidiabetic agents) which may improve diabetes control and help reduce the incidence of some of its associated complications.

Studies on costs of diabetes take into consideration the medical care costs for maintaining glycemic control, treating short-term and long-term complications and treating other comorbidities. However, given the large number of cost drivers associated with diabetes care [16], researchers found it difficult to reach a uniform method for predicting its cost.

This chapter presents a review of the published literature reporting on the costs of diabetes and its associated complications. An electronic literature search of relevant databases (including PubMed, HealthSTAR, EMBASE, EconLit, and Cochrane Library) was conducted for papers published between 1966 and March 2001, limited to the English language. A more detailed list of the databases searched, key words used, and number of hits is presented in Appendix 1.

After a preliminary scanning of all citations, only articles published between 1990 and present were selected as significant environmental changes (such as aging of the population and health care reforms) took place in the late 1980s and early 1990s. Also, many changes in the methodologies used for cost of diabetes studies occurred during this period [74, 88, 89]. However, papers published before 1990 were cited where appropriate. Additional articles were found by reference tracking.

Given the objective of the present study, the literature search focused on descriptive cost studies that reported on cost drivers for diabetes care. This review was limited to studies on cost of diabetes that reported on patient-level data. The aim was to summarize findings reported by studies that comprehensively assessed costs of diabetes and used predictive modeling approaches to risk stratify their patients. Excluded were studies that estimated only indirect costs of diabetes care. Economic evaluations of health care interventions designed and used for diabetes control and management were also excluded.

Diabetes: clinical burden of the disease

Diabetes mellitus is a chronic metabolic disease caused either by deficiency in production of insulin by the pancreas or by ineffectiveness of the insulin produced [68, 83, 84]. Such a deficiency results in increased concentration of glucose in the blood (hyperglycemia), which leads to damage to many of the body's systems, especially the blood vessels and the nerves. The two main forms of diabetes are type 1 diabetes (previously referred to as insulin-dependent diabetes mellitus or IDDM) and type 2 diabetes (previously referred to as non-insulin dependent diabetes mellitus or NIDDM). In type 1 diabetes the pancreas fails to produce the insulin, and type 2 diabetes results from the body's inability to respond properly to the action of insulin produced by the pancreas. Type 2 diabetes is much more common and accounts for about 90% of all diabetes cases worldwide [28, 49, 68, 70, 84, 92].

Type 1 and type 2 diabetes differ in various ways. Patients with type 1 diabetes are thin, the onset of disease is relatively acute, they cannot live without insulin supplementation and are prone to ketoacidosis [28, 68, 83, 84, 86, 90, 92]. This form develops most frequently in children and adolescents. Prevalence rates of type 1 diabetes vary among countries [38, 40, 86, 92].

Type 2 diabetes occurs principally in adults (often in obese people) and is rarely associated with ketoacidosis [28, 41, 68, 70, 84, 92]. Its true prevalence is uncertain because of the delayed diagnosis and problems of definition, particularly with increasing age [41, 92]. Estimates therefore vary widely. Type 2 diabetes is insidious, in that the patient may remain asymptomatic for years while irreversible long-term diabetes-associated complications develop [28, 33, 44, 72, 83, 96]. The United Kingdom Prospective Diabetes Study (UKPDS) reported that half of the people newly diagnosed with type 2 diabetes already had one or more of the complications or comorbidities associated with diabetes [97].

Magnitude of the problem

Diabetes is a serious disease, which is becoming increasingly common worldwide. Using the data available from published prevalence studies, the WHO has estimated that diabetes affected 30 million people in 1985, 135 million people in 1995 and predicted a rise to approximately 300 million people by the year 2025 [3,102]. Its prevalence approaches 8% of the adult population in the United States and much of Europe [2, 28, 62, 65, 70]. Much of diabetes may be undiagnosed [88, 92]. American survey data indicated that approximately 35% to 44% of all diabetes cases may be undiagnosed, depending on the test used to diagnose diabetes [28]. The prevalence rises with age (up to 10% of the population of 65 years and over) and is also higher in certain ethnic groups (Indian/Aboriginal, Black and Hispanic populations) [28, 39, 62, 70, 92].

It has been suggested that the apparent increasing prevalence of diabetes (particularly of type 2 diabetes) is due to demographic changes (the aging of the population, increased survival of people with diabetes, and changes in the ethnic composition of countries worldwide), lifestyle changes, and new diagnostic criteria [9, 28, 43, 66, 68].

Morbidity and mortality

A diagnosis of diabetes immediately increases the risk of developing various clinical complications that are largely irreversible [30]. Duration of diabetes is an important factor in the pathogenesis of complications but other risk factors and conditions interact with diabetes to affect the clinical course of these complications [30, 60, 83]. Both main types of diabetes are associated with complications, which may be acute or chronic. People with diabetes also appear to be at increased risk for general medical conditions other than acute and chronic complications associated with diabetes.

The onset of diabetes-associated complications is frequently the first indication of the disease [40]. One of the acute complications is diabetic ketoacidosis, a metabolic disturbance with potential fatal consequences, which mainly affects people with type 1 diabetes [40, 59, 86, 92]. Another severe acute diabetic condition is hypoglycemia, which is frequent in insulin-treated subjects [40, 86]. Chronic complications are mainly due to micro-vascular and macro-vascular diseases caused by diabetes. In the longer term, hyperglycemia causes irreparable damage to the blood vessels, the heart, kidney, eyes, and nervous system and represents a major threat to the health and life of those suffering from diabetes [28, 40, 70, 83]. Many of these complications take 5-20 years to develop.

Micro-vascular complications involve small blood vessel damage caused by hyperglycemia leading to retinopathy (eye disease), nephropathy (kidney disease), and neuropathy (nervous system disease) [28, 40, 83]. Proliferative diabetic ***retinopathy*** is a severe complication of diabetes that can lead to blindness [28]. It occurs in 40% of those taking insulin and 5% of those not taking insulin [28] and is the leading cause of blindness and visual impairment in adults [21, 28, 40, 59, 72, 83, 86, 89, 92]. The proportion of blindness attributable to diabetes varies between 26% in people with type 2 diabetes and 94% in people with type 1 diabetes [40]. Of people who have had diabetes for at least 15 years, 97% of those taking insulin and 80% of those not taking insulin have retinopathy [28]. Twelve percent of people who have had type 1 diabetes for ≥30 years are blind [28].

Diabetes is also a leading cause of diabetic ***nephropathy*** [21, 40, 83]. It is responsible for up to 40% of end-stage renal disease (ESRD) or kidney/renal failure, which requires dialysis or renal transplantation [9, 59, 73, 83, 86, 89]. ESRD is the main cause of death among people with

type 1 diabetes but the risk of ESRD is also very high among people with type 2 diabetes (particularly in some ethnic groups) [28, 38, 40, 86, 92].

Between 50% and 70% of the people with diabetes have some degree of ***neuropathy*** which can lead to sensory loss with risk of gangrene and foot amputation, especially when combined with macro-vascular disease [28, 30, 40, 59, 72, 83, 86, 92, 93, 98]. In half of these patients it develops within nine years of diagnosis [28]. Diabetes is the most common cause of non-traumatic foot amputation [21, 73, 89]. The risk of lower extremity amputations following diabetes diagnosis is 6% at 20 years and 11% at 30 years [28].

Macro-vascular complications involve large blood vessels such as coronary, cerebral or peripheral vessels and include coronary heart disease, stroke and peripheral vascular disease [28, 40, 83, 91]. The development of these diseases is accelerated with type 1 diabetes and often present at diagnosis of type 2 diabetes [83, 96, 97]. There is evidence to suggest that people with diabetes are 2-6 times more likely to suffer from heart disease or stroke [28, 30, 40,73,83, 92]. At least half of the patients with diabetes are affected by hypertension (high blood pressure) [30], which is a risk factor for most complications of diabetes [28]. Hypertension is associated with reduced survival, the predominant cause of death being myocardial infarction in 40% of cases [83]. Ischemic heart disease accounts for 50% of deaths and stroke for 15% of deaths in patients with type 2 diabetes in developed countries [59]. Cardiovascular disease (CVD) is a major cause of death for people with diabetes [30, 40, 86, 89, 92].

As a result of the disease and the associated morbidity, people with diabetes have more frequent and intensive encounters with the health care system. Overall, the complications of diabetes increase the yearly incidence of hospitalizations and negatively affect the individual's health status [28, 59, 98]. Disability rates are higher in patients with diabetes. Data from the United Kingdom showed that one half of all patients with type 2 diabetes report limitations related to a physical impairment or other health problems, 20% are unable to carry on their major activity and 22% report having restricted activity days within every two-week period [98]. Foot ulceration is the leading cause of hospital admission for patients with diabetes [83].

Diabetes is the fourth leading cause of death in most developed countries [74]. It is rarely mentioned on death certificates as a cause of death, and the number of deaths directly attributable to diabetes is not easy to quantify although it is generally acknowledged that affected people have a reduced life expectancy [40, 59, 62, 65, 92]. According to United States data, people with type 1 diabetes have a minimum 15-year reduction in life expectancy [28]. Adults with diabetes have an annual mortality of about 5.4% (double the rate for non-diabetic individuals) and their life expectancy is decreased on average by 5-10 years [30]. Although the

increased rate is largely due to cardiovascular disease, deaths from other causes are also increased.

Diabetes: economic burden of the disease

Costs of diabetes

The costs of diabetes are numerous and their presentation is usually divided into direct, indirect and psychological categories. Direct costs include medical and non-medical costs (such as costs borne by patients and their families in seeking diabetes care). Medical care costs attributable to diabetes consist of all expenditures associated with the daily treatment and control of the disease and with the prevention, treatment, and control of its related complications and comorbidities. They include costs of hospitalizations, outpatient visits, medication, equipment, and devices for blood/urine glucose tests and monitoring, as well as the costs of the prescribed diet. Indirect costs are associated with production losses due to short-term illness, early retirement, and premature death. Psychological costs include factors such as the effect of the illness on the quality of life of the patient.

The economic consequences of diabetes have been reported by many studies using cost-of-illness estimates, the most widely used assessment technique in diabetes research. Cost-of-illness studies are descriptive studies which quantify all costs related to a particular disease or event without comparing alternative uses of resources. Their value has long been debated and, although their usefulness has been questioned, they can provide information that can serve as a baseline for subsequent economic evaluation [29, 40, 47, 95].

Much of the work describing the cost of diabetes was eloquently summarized in several reviews [52, 59, 60, 61, 62, 74, 86, 87, 88, 89, 92]. Their findings generally agreed upon the following:

- Most of the existing published estimates are specific to the United States experience, but a number of reports have emerged recently from other countries [2,14, 54, 55, 93, 94].
- The majority of the economic data on cost of diabetes have been based on national health, health care, disability, and mortality statistics. National statistics were often broken down by diagnostic categories based on the International Classification of Diseases (ICD) codes.
- To determine costs of diabetes from diagnostic category data, studies used general computational methods such as top-down or bottom-up approaches or combinations of these two methods.
- Most investigators have failed to distinguish between the two main types of diabetes and comprehensive and accurate cost data specific to type 1 or type 2 diabetes are lacking. The main reason is the inability to distinguish between patients with type 2 diabetes and those with type 1 diabetes in diagnostic or ICD coded information.

- In general, data were attributed to diabetes only when it was listed as the primary diagnosis or reason for a health care visit, disability or cause of death. This raised concerns about the underestimates reported by these studies, which missed the health care costs incurred by individuals where diabetes was a secondary or tertiary factor. Few studies have included diabetes as a secondary diagnosis.
- Most published studies have tended to focus on direct costs (such as costs associated with inpatient and outpatient care and with medication) in their analyses because they are easily recognizable and the easiest to measure. Few studies included indirect costs because they are less obvious and it is difficult to allocate monetary values to their components. Psychological costs were sometimes mentioned in cost analyses but usually dismissed because of the difficulties involved in assigning costs to factors such as the major alteration in lifestyle, which might be necessary for people with diabetes.

The cost estimates of diabetes care published by the cost-of-illness studies provide a general idea of the costs attributable to diabetes and its complications [52, 59, 60, 61, 62, 74, 86, 87, 88, 89, 92]. They are in broad agreement that:

- The costs of diabetes care are quite substantial and growing. By implication they might be reduced if diabetes and/or its complications could be prevented or treated more effectively. Songer et al. [89] suggested that the increase in the prevalence of diabetes and the changes in the methodologies on the cost estimates, especially due to the inclusion of diabetes as a secondary diagnosis, might explain the increase noted over time in the cost estimates of diabetes in the United States.
- Most of the associated excess costs were health care costs for patients who developed chronic complications. The complications that accounted for significant health care costs were cardiovascular and renal diseases, visual and foot problems, and neuropathy.
- The costs associated with hospitalization of patients with diabetes represented a high percentage of the total costs of diabetes care. Cardiovascular disease and foot problems accounted for a high proportion of costly hospital admissions and disability.
- The estimated total cost of diabetes can be attributed approximately in equal percentage between direct and indirect costs.

However, there are limitations to the interpretation of these cost estimates [52, 59, 60, 61, 62, 74, 86, 87, 88, 89, 92]. They differ and comparisons among studies are difficult to make. These estimates are not directly comparable because:

- Different methodologies and assumptions were used in these studies. The frameworks of the analyses differed as well.
- Diabetes care components considered in the direct cost calculation varied between the studies. Most studies included costs associated with hospital care, physician services,

and prescription drugs. However, there were discrepancies with respect to the inclusion of costs associated with nursing home care, emergency department services, home health care, and others. In some studies, it was unclear what had been included and what had been left out.

- Most of the studies attempted to capture all of the costs of those complications due to diabetes but not all completely captured the costs of chronic complications. These studies differed in the availability of various data sources. Also, the inclusion and exclusion of various complications and comorbidities in the analyses resulted in considerable differences in the estimated economic impact of diabetes. These differences may be or may not be significant based on the prevalence of the diabetes-related clinical conditions in question.
- The published estimates were specific to the country in which the work was carried out since supply, availability, prices, and consumption of health care services as well as collection of data differ from one country to another. Hence, valid and reliable cost comparisons among countries are not feasible and extrapolating cost data from one health care system to another is problematic because methods of care delivery and funding are different.
- Also, the estimates were specific to the year in which the study was performed and the specific group of patients studied (which were different in terms of demographic and clinical characteristics).

Consistent with findings from epidemiological studies, the results reported by the cost of diabetes studies increasingly acknowledged that complications such as retinopathy, neuropathy, nephropathy, and cardiovascular disease represented the principal clinical and economic burdens of the disease. These studies serve to illustrate the impact of these complications on health care. Therefore, therapies aimed at preventing or delaying the occurrence of these complications and at controlling them in case they are present are of primary importance. Given the ever-increasing costs of diabetes care and the introduction of new therapies it is important to determine the net impact of these complications on the health care resource use and costs, based on a complete assessment that includes all economically relevant events.

Based on the published evidence in the diabetes literature, it may be expected that known predictors of morbidity and mortality in diabetes tend to determine the utilization of health care services and the associated costs. The utilization of health care services is a function of many variables including demographic and clinical factors (age, gender, race, disease severity, and health status) and other factors such as income, education, behavioral factors (coping), and structural factors including access to care and type of insurance coverage [35].

Given the clear identification of the independent prognostic factors and the inter-individual variation in the disease severity it is appropriate to estimate costs of diabetes care at individual level.

The study of costs associated with the use of health services for diabetes care is challenging for a variety of reasons; such as the insidious onset of type 2 diabetes, the diverse range of vascular complications that can result from all forms of diabetes, and the complexity of multiple and interrelated risk associations. Pagano et al [74] suggested that investigation of the overall costs of diabetes is not important because the pathology of the disease is complicated and progressive. Since patients at different stages of disease severity are likely to require different levels of resource consumption associated with different costs of care [86], identification of subgroups of patients according to clinical and economic criteria may give a more precise and worthwhile analysis [74].

However, most of the current estimates are broad in perspective and the nature of the cost data on specific subgroups such as age, gender, race, disease type, and severity are preliminary [74, 89]. Despite the existence of the initiatives that focus on treating and reducing the impact of diabetes complications the costs of each specific complication has not been estimated [89]. The existing comprehensive estimates (which examined the many costs associated with diabetes and its complications) have been provided on an aggregate level (national-level spending rather than patient-level costs) [49]. These estimates demonstrate the magnitude of the total costs associated with the disease but may not be readily translated into patient-level cost inputs for an economic evaluation of new medical therapies and interventions aimed at preventing or delaying complications. Although recently published studies examined patient-level cost data [5, 7, 23, 71, 73, 77] they reported estimates only for individual complications or only for selected components of diabetes care.

An understanding of the underlying cost distributions for diabetes care could help in targeting interventions, integrating disease-management, and managing the formal structure of the health care plan being considered. Therefore, recognizing the principal cost drivers for diabetes care provides a foundation for the development of disease-management initiatives, resulting in utilization of best practices and improved outcomes.

Cost predictions of diabetes care

The estimation and prediction of health care costs for a specific population over well-defined time periods are used in many contemporary pharmacoeconomic investigations [13, 63]. Traditionally, the research has relied upon medical records and/or patient-derived data. Recently the growing availability of large administrative and clinical datasets offered

opportunity for estimation of multivariable cost functions that yield disease cost forecasting at the individual level, conditional on interventions, patients' characteristics, and other factors [63]. Despite the limitations of claims data, the use of large administrative databases as a research tool has gained increasing popularity, that can be due to timely availability, the large patient populations they cover, low cost, and applicability in the real world [13, 35].

The determination of health care cost functions used to identify the cost drivers of health care for patients with diabetes is becoming increasingly sophisticated through the application of statistical techniques. To date, several published studies have used predictive modeling approaches to risk stratify patients within various disease states of diabetes, with or without certain complications [10, 15, 37, 42, 58, 79, 101]. The following section summarizes these studies and their reported findings. Table 2.1 (see Appendix 2) summarizes the main characteristics of the seven studies reviewed.

Cost prediction studies

The study by **Bhattacharyya and Else** [10] used retrospective claims data (calendar year 1995) to estimate the relative impact of health care services and patient-specific variables on the medical costs of treating patients with type 2 diabetes. The main objective was to determine and analyze the principal cost drivers for treatment of patients enrolled in a managed care organization. Other objectives included estimating the marginal influence of various factors on the medical costs of treating type 2 diabetes; and establishing the usefulness of implementing an ordinary least squares (OLS) regression model via an integrated claims database to identify costs of a disease state.

The medical claims data included paid claims for services and procedures for diabetes and commonly associated co-morbidities. Claims and associated costs for pharmacotherapy administered to the patient population were recorded in the pharmacy data. The study included 5,171 patients. Patients aged $\geq$ 65 years were excluded because Medicare claims were unavailable for this population.

A regression model was employed to identify the principal cost drivers of the identified cohort to the managed care system. Independent variables included presence/absence of some commonly observed co-morbidities (hypertension, hyperlipidemia, cardiovascular disease, congestive heart failure, renal disorders, retinopathy, neurologic disorders, and any cardiac or non-cardiac co-morbidity combinations), therapy variables, a number of significant events (hospitalization, dialysis, haemoglobin A_{1c} (HbA_{1c}) testing, and eye examination), patient enrollment category (fee-for-service vs. capitated system), and patient age and gender. The dependent variable was the natural logarithm of total medical costs of treatment for diabetes and commonly observed co-morbidities.

The results showed that among co-morbidity variables, the three largest treatment cost drivers for patients with type 2 diabetes, in decreasing order of significance, were the presence of neurologic disorders, renal disorders, and any co-morbidity combination (cardiac or non-cardiac or both). Higher costs of treatment were also associated with episodes of hospitalization, use of antidiabetic medication, dialysis services, and HbA_{1c} testing. Whether the patient was being treated under a capitated provider payment system of a fee-for-service system did not have any significant impact on the medical costs of diabetes-related treatment. Age was positively associated with these costs, indicating that older patients were more likely to incur higher costs to the system. The overall explanatory power of the regression model was 40%.

Brown et al [15] analyzed nine years of clinical data (1987-1995) on 11,768 subjects (aged 30 years and over) who had "probable" type 2 diabetes, were members of a large health maintenance organization (HMO) in the United States, and had a 12-month eligibility in 1995. Investigators ascertained the presence of cardiovascular disease and renal complications, staged the members' progression, and estimated their incremental costs by stage. They used two ordinary least squares regression models. One was used to regress the annual cost per person on the complication stage, age, and sex. In the second model, interaction terms between the three stages of cardiovascular disease and all four stages of renal disease were included.

No statistically significant differences between men and women in the prevalence and staging of complications were found [15]. Per-person costs increased over baseline ($2,033) by more than 50% after initiation of cardiovascular drug therapy and/or use of a cardiologist, and by 360% after a major cardiovascular event. Abnormal renal function increased costs of diabetes treatment by 65% ($1,337 USD). Advanced renal disease increased costs of diabetes treatment by 195% ($3,979 USD) and ESRD by 771 % ($15,675 USD). Both cardiovascular and renal diseases were more common among older subjects.

Age was a non-significant predictor of costs of complications and did not affect the additional costs of these complications [15]. Women had substantially higher medical care costs after controlling for age and presence of complications. Of the interaction effects that were statistically significant, most were small, less than $1,000 USD. The one exception involved subjects in the highest stage of both complications considered. They exhibited substantially higher costs ($3,734 USD) than would have been expected without the interaction. The investigators concluded that in an aggregate population, the greatest cost savings would be achieved by preventing major cardiovascular events. For individuals, the greatest savings would be achieved by preventing progression to stage 3 renal diseases.

Gilmer at al [37] examined the relationship between baseline levels of hemoglobin A_{1c} (HbA_{1c}) and medicare charges over 3 years (from 1993 to 1995) in a health maintenance organization (HMO). Their study included 3,017 adults (aged 18 years and over) with type 2 diabetes. The diagnosis of diabetes was ascertained from diagnostic and pharmaceutical databases. Multiple linear regression analysis was used to estimate the relationship between glycemic control and the cost and intensity of care for patient with diabetes. Three years of total charges (for inpatient and outpatient services) was the dependent variable and demographic characteristics (age, sex), HbA_{1c} level, and clinical characteristics (chronic conditions such as hypertension, coronary heart disease, lipid disorder) were the independent variables.

The investigators found that medical care charges increased significantly for every 1% increase in HbA_{1c} above a level of 7% over 3 years [37]. They were closely related to the HbA_{1c} level before and after adjustment for age, sex, coronary heart disease, and hypertension. Standardized 3-year estimates of charges ranged from $10,439 for patients without comorbid conditions to $44,417 USD for those with heart disease and hypertension. For patients with diabetes only or with diabetes plus other chronic conditions, the rate of increase in charges with HbA_{1c} levels was consistent. The most substantial charge increments occurred in patients with diabetes in combination with heart disease and hypertension.

The model by Gilmer et al [37] suggested that the baseline HbA_{1c} level was a powerful predictor of subsequent health care charges and that savings should be greatest among those with the worst baseline levels. It suggested savings of approximately $400 to $4,000 (USD) per patient, with the savings increasing with the level of baseline HbA_{1c} and the presence of vascular disease.

Guo et al [42] conducted an investigation to determine total direct costs of health care for patients with diabetes and to study the influence of different factors affecting the costs. They also examined each type of service (e.g., hospitalization, outpatient care, prescription drugs, physician encounters, and laboratory tests) to provide evidence about the relationship between patients' health care utilization and the related predictors. The study included a total of 7,931 patients (aged 65 years and younger) with a diagnosis of diabetes in the fiscal year 1992, who were alive on October 1st 1995 and continuously eligible for Alabama Medicaid Program.

Using data from Medicaid claims, multiple regression, and canonical correlation methods were used to analyze the patients' direct cost-of-illness including the costs associated with each health care service used by each patient. The direct costs included the cost for hospitalization, physician encounters, laboratory tests, prescription drugs, outpatient care, and

other health care services. The independent variables included age, sex, race, dwelling, type of diabetes mellitus, diabetic complications (neurologic, cardiovascular, endocrine/metabolic, renal, and other complications), number of prescribers visited, number of comorbidities, therapy, and emergency department visits.

The costs of hospitalization, outpatient care, prescription drugs, and physician encounters were the four largest components of the direct costs for Medicaid patients (comprising 29.9%, 21.3% and 14.3% of the costs, respectively) [42]. After controlling for other factors, the direct costs for a patient with IDDM was $5,160 USD higher than for a patient with NIDDM during the study period. The cost for a patient with renal dysfunction was $59,920 USD higher than for other patients with diabetes. Each increase in the number of different prescribing physicians per patient was associated with a cost increase of $450 USD. Each, additional, comorbidity increased the cost by $735 USD per patient. The cost for a male patient was $2,140 USD higher than that for a female patient. The cost for a caucasian patient was $1,330 USD higher than that for non-caucasian patient. For a patient who relied on diet there were $2,750 USD reduction in costs compared with other patients during the study period. More than 20% of the variability in patient's health care utilization costs was explained by the set of predictive factors.

The results showed that the direct costs and health care utilization for Medicaid patients with diabetes were significantly accounted for by the number of comorbidities, the number of different physicians visited, IDDM, and complications (especially renal dysfunction). Patients who relied on dietary therapy and exercise to control diabetes had lower health care costs and utilization than the other patients. The authors suggested that significant amounts of health care costs and utilization might be controlled or reduced if diabetes management could be successfully aimed at preventing associated complications, controlling comorbidities, and minimizing the number of different physicians visited.

Krop et al [58] conducted a prospective cohort study of health care costs and utilization by diabetic patients from a random sample of aged Medicare beneficiaries in United States from 1994 to 1996. They examined all services covered by the Medicare program. The objective was to describe the health care costs and utilization pattern among older adults with diabetes and examine factors associated with expenditures over a 3-year period. The study compared beneficiaries with diabetes in 1994 (n=169,613) to those without diabetes (n=968,832).

Multivariate linear regression analysis was used to assess the contribution of patients' demographic and clinical characteristics in 1994 on Medicare Part B, inpatient, and total expenditures in 1995 and 1996 [58]. Expenditures included costs associated with hospital inpatient and outpatient services, physician and suppliers (Medicare Part B) and skilled

nursing facilities. The independent variables included age, sex, race, Medicaid eligibility, diabetic complications (cerebrovascular disease, peripheral vascular disease, amputation, ischemic heart disease, congestive heart failure, nephropathy, retinopathy, neuropathy, and diabetes-related infections), comorbidities (specific conditions, other than those included in the list of diabetes-related complications), and prior health care utilization (number of emergency room visits and average hospital length of stay).

The per capita expenditures for beneficiaries with diabetes were 1.7 times greater than those for beneficiaries without diabetes in 1994 [58]. This ratio remained fairly constant over the two-year follow-up. The regression model was able to explain 7% of the variation in total expenditures in 1995 and 6% of the variation in 1996, and 10.7% of the variation in Part B expenditures in 1995 and 8% in 1996. Baseline demographics and presence/absence of Medicaid eligibility explained very little of the variation in Part B, inpatient and total costs in 1995 and 1996.

By adding diabetes-related complications, the model was able to predict seven times more of the variation in costs in 1995 and 1996. Adding comorbidities and utilization of services into the model slightly improved the ability to predict costs for both 1995 and 1996. Overall, the ability to predict expenditures was better over one year than over two years. Also, all models were better at predicting Part B expenditures than either inpatient or total expenditures.

The authors concluded that patients with diabetes are consistently more expensive than those without diabetes. Demographic and clinical factors at baseline are able to predict only a small portion of future expenditures among this population. In addition, the most expensive patients in one year were often not the most expensive in subsequent years.

Ramsey et al [79] conducted a retrospective cohort study in a large HMO to develop incidence-based estimates of the cost of several diabetes-related complications. The study included a total of 8,905 patients with type 1 diabetes (IDDM) and type 2 diabetes (NIDDM) and 36,520 age- and gender-matched controls without diabetes, all observed from 1992 to 1995. Incidence rates of six major diabetes-related complications were computed for both populations. The goal was to compare expenditures for individuals: (1) having diabetes and relevant complications, (2) having diabetes without the complication, (3) without diabetes but with the complication, and (4) individuals with neither diabetes nor the complication. The incremental costs for each complication (attributable costs) were computed as ratios of total annual health care expenditures for individuals with diabetes with a complication compared with those without diabetes and without the complications (considered the baseline group).

Multiple regression analysis was used to predict medical expenses for cases and controls for the 1st and 2nd year following diagnosis. The dependent variables were annual health

expenditures (including costs associated with the medical staff, nursing, pharmacy, laboratory, radiology, hospital inpatient and community health services) in the 1st and 2nd year following diagnosis. Independent variables included dummy variable representing the four categories noted above, as well as age and comorbidity as measured by the presence of chronic diseases other than the condition of interest.

Over 3 years, the incidence rates of the six major complications were higher for the group with diabetes when compared with the control group (myocardial infarction: 9.0 vs. 3.2%; stroke: 8.7 vs. 3.8%; hypertension 26.2 vs. 16.9 %; ESRD 5.9 vs. 1.4%; foot ulcer 7.9 vs. 1.1 %; and eye disease: 44.3% vs. 2.8%, respectively). The excess costs for the 1st year following diagnosis were 1.59 for patients with no complication, 4.1 for patients with myocardial infarction, 3.5 for those with stroke, 2.56 for those with hypertension, 4.32 for ESRD, 4.0 for those with foot ulcer, and 2.46 for those with eye disease. For younger cohorts (less prevalent in the sample), incremental costs for each complication were generally greater than in the older group.

Wagner et al [101] attempted to determine whether sustained improvements in HbA_{1c} levels among patients with diabetes were followed by reductions in health care utilizations and costs. They conducted a historical cohort study in an HMO, which included all patients (aged 18 years and over) entered into an automated diabetes registry (based on specific criteria), continuously enrolled between January 1992 and March 1996, receiving care from the HMO physicians and with HbA_{1c} measured at least once per year in 1992-1994 (n=4,744). Patients classified as "improved" (n=732) were those whose HbA_{1c} levels decreased (1% between 1992 and 1993) and sustained the decline through 1993. The remaining patients (n=4,012) were classified as "unimproved". The HbA_{1c} levels at baseline in "improved" patients were higher at baseline than the measurements for "unimproved" patients (10.0% vs. 7.7%, respectively; $p<0.001$).

Multiple linear regression analysis was used to estimate the relationship between glycemic control and the cost and intensity of care for patient with diabetes (improved vs. unimproved patients in 1992-1997) [101]. Data on patients' demographics, HbA_{1c} levels, treatment, complications, costs, and health care utilization were collected from administrative data systems. Total direct health care costs included direct and overhead costs associated medical staff, nursing, pharmacy, laboratory, radiology, hospital inpatient, and community health services. Presence at baseline (any mention in 1992 or 1993) of six major diabetes-associated complications (foot ulcer, retinopathy or macular edema, hypertension, ischemic heart disease, myocardial infarction, and stroke) was derived from inpatient and outpatient diagnostic codes. Costs and utilization estimates were adjusted for age, sex, baseline HbA_{1c} level, and baseline presence of any of the six complications.

The reported results showed that the mean total health care costs were $685 to $950 (USD) less each year in the improved cohort for 1994 (p=0.09), 1995 (p=0.003), 1996 (p=0.002) and 1997 (p=0.01) [101]. The cost savings were statistically significant only among those with the highest baseline HbA_{1c} level (10%) for these years and appeared not to be affected by the presence of complications at baseline. The authors concluded that a sustained reduction in HbA_{1c} level among diabetic adults is associated with significant cost savings within 1 to 2 years of improvement.

Discussion on the cost prediction studies

In the studies described above, investigators have attempted to identify health care cost drivers by using predictive modeling approaches such as multivariate regression analyses. The reported findings suggested that direct cost-of-illness and health care utilization for patients with diabetes are influenced by certain demographic and clinical factors (see Table 2.1 in Appendix 2). All studies were conducted in the United States and most included large cohorts of patients with diabetes enrolled in Health Maintenance Organizations located in different parts of the United States [10, 15, 37, 79, 101]. The cohorts differed with respect to age, race, and type and severity of diabetes.

Common to all regression models used in these studies is a mathematical function, which captured the impact of explanatory variables on direct costs of health care for patients with diabetes. This approach allowed conditional prediction of costs at the patient level. In most studies, total costs/charges included the costs/charges estimated for hospitalization, physician services, and prescription drugs [10, 15, 37, 42, 79, 101]. Data for the explanatory variables were obtained from medical and pharmacy claims (for different calendar years) for patients defined as having diabetes based on different criteria. Investigators applied logarithmic transformation to the cost variable to avoid the difficulty in analysis associated with the strongly right-skewed cost data [63].

Most studies used age and sex/gender as variables defining the patient [10, 15, 42, 58, 79, 101]. Few studies used race [42, 58] and therapy [10, 42] as explanatory variables and one study [42] used patient geographic location variables. The models used dummy variables to indicate a history of specific chronic complications and comorbidities (defined as commonly observed and mutually exclusive complications and comorbidities associated with diabetes, using different criteria and decision algorithms), type of antidiabetic therapy, previous use of health care services, type of physician reimbursement plan, and eligibility for specific health insurance plans.

Most studies reported statistically significant positive associations between the costs/charges of diabetes care and disease severity as measured by presence/absence of specific diabetes

associated complications and/or comorbidities (including cardiovascular, renal, and neurologic diseases, as well as foot problems and retinopathy). The investigators separately identified some complications in order to estimate the additional cost of each specified complication. Some studies also identified age, sex, race, and therapy variables as statistically significant predictors of costs of diabetes care for their study populations (see Table 2.1 in Appendix 2).

Diabetes in Canada

Clinical burden

Diabetes is a significant public health problem of potentially enormous proportions in Canada today. Recently, it has been estimated that the number of Canadians aged 12 years and over with diabetes is 1.2 to 1.4 million (4.9% to 5.8%), including undiagnosed cases of diabetes [28]. The prevalence increases with age, with diabetes diagnosed in 3% of people aged 35 years to 64 years and in 10% of people aged 65 years and over. It has been estimated that approximately 60,000 new cases of diabetes are diagnosed in Canada (an incidence rate of 2.6 new cases per 1,000 people among those aged 12 years and over) every year [28].

Recent Canadian survey data suggest a trend towards increased prevalence of diabetes [28]. The number of Canadians with diabetes can be expected to increase as the population ages, rates of obesity rise and survival of patients after diagnosis increases due to improvement in treatment and management of the disease. The prevalence of diabetes is expected to increase two percentage points by 2025 [56].

Government reports and research studies have identified Canadian Aboriginal or First Nations populations as having very high diabetes prevalence rates [11, 12, 24, 28, 34, 45, 76, 104, 105]. It appears that age-standardized diabetes prevalence rates are triple those found in the general population and it has been estimated that 60,000 people have diabetes, including undiagnosed cases [28]. Reported rates are higher in women and in some Aboriginal communities [24, 28, 76].

In Canada, diabetes is ranked as the seventh leading cause of death based on mortality data (5,447 deaths) and it accounted for 25,000 potential years of life lost due to premature death (prior to age of 75 years) in 1996. [28]. It is a noted risk factor for cardiovascular disease and the most common cause of new onset blindness in the working age population, of end-stage renal disease, and of lower limb amputations [28]. However, Canadian data on the complications of diabetes are limited. Current data sources provide estimates of the proportion of people who have diabetes and who also have heart disease, vision problems (not specifically retinopathy), and kidney failure, for which diabetes is likely to be a contributing cause.

According to 1996 National Population Health Survey data (NPHS 1996), Canadians have 2 to 6 times (depending on age) the likelihood of having heart diseases or stroke if they have diabetes compared those without diabetes [28]. Heart disease is uncommon in those under 30 with type 1 diabetes. The greatest difference is in the 35 to 64 years age group (the overall prevalence is 16.2% among people with diabetes vs. 3% among those without diabetes). An estimated 40% of people with diabetes in Canada have high blood pressure, one of the main risk factors for cardiovascular disease. Among First Nations population it has been estimated that 43% of adults with diabetes have hypertension compared with 10% of those without diabetes.

The proportion of vision loss is not known at the national level [28]. However, people with diabetes aged 65 years and over reported significantly higher rates of vision problems than did their peers without diabetes. There were reports of significantly higher rates of cataracts (21.9% vs. 14.1%, respectively), vision problems that cannot be corrected (9% vs. 5%, respectively), and glaucoma (7% vs. 5%, respectively).

According to the Canadian Organ Replacement Register (CORR) data, the proportion of patients with newly diagnosed kidney failure who also have diabetes increased from 16% in 1981 to 29.6% in 1996 [18, 19]. The report indicated that there were 3,340 people with diabetes as of December 1996 who were receiving treatment for ESRD. Statistics released in 2000 by the Canadian Institute for Health Information from the CORR [19] showed that the rate of patients with diabetes on dialysis was 39.2 per million in 1998 (1,190 patients). The 10-year survival rate among diabetic patients receiving dialysis was 20% lower than that of persons without diabetes.

The prevalence of diabetic nephropathy among Aboriginal Canadians is much higher than that in the general population, with rates ranging from 25% to 60% after 15 to 20 years with diabetes [28]. It has been estimated that an Aboriginal person in Manitoba is 12 times more likely to have diabetic nephropathy than a non-Aboriginal person. Among First Nations people in Manitoba the risk of ESRD (with more than half of cases caused by diabetes) is approximately four times higher than of other Manitoba residents, and the relative risk of undergoing dialysis is 6.5 times that of non-Aboriginal persons.

Diabetes has been associated with more frequent disability days and increased loss of productivity. Among the working age population (35 years to 64 years), 23% of people with diabetes in Canada had one or more disability days in a two-week period, compared with only 11% of those without diabetes [28].

Economic burden

In Canada, diabetes is a chronic disease with major long-term implications for the health and well being of affected individuals, but also for the costs to society as a whole [28, 69, 92]. People with diabetes are heavy users of health care services (particularly of hospital and physician services) [28, 69]. Although since 1985 awareness has been raised of the large economic burden of diabetes in Canada and the lack of data sufficiently developed to allow comprehensive costing of the disease [22], only a few studies have attempted to estimate the economic consequences of diabetes in Canada [8, 57, 67].

In 1993, the economic burden of diabetes alone was estimated at $1.1 billion annually [28]. This was considered to be an underestimate because costs of associated complications, such as cardiovascular disease and renal failure were not included. The economic burden of diabetes and its complications has been estimated to be up to $9 billion (USD) annually in direct health care costs, including lost productivity due to diabetes–associated illness and related premature death [28]. However, these estimates were based on limited survey data and extrapolations from American studies and may not accurately represent the true burden of diabetes in Canada. Comprehensive and accurate data on the economic burden of diabetes and its complications in Canada are still lacking. This review confirms earlier findings [92] that although there have been numerous attempts to quantify the costs of diabetes in other countries, no comprehensive study has been carried out for Canada and the provinces. Also, the existing information is outdated.

Summary

Although many discrepancies exist among the published studies on cost of diabetes, all agree that costs of diabetes are extensive and growing. Because diabetes is a chronic disease affecting a large number of different organ systems in the body and many acute and chronic health problems can be directly attributed to it, health care utilization and costs are higher in affected individuals compared to the general population. A large share of the costs of diabetes care arises as a consequence of an excess prevalence of associated chronic conditions, particularly those related to neuropathy, nephropathy, retinopathy, and cardiovascular diseases.

The existing estimates of total costs of health care for diabetic patients provide useful information for understanding the macro implications of the disease in the dynamic health care systems. However, there are still few studies that comprehensively address the major complications associated with diabetes, although they have been increasingly identified as the most important contributors to the costs of diabetes care. Still little is known about what

happens to these costs over time. Also, there is still little information regarding which of the various independent prognostic factors predicts future increased health care expenditures among patients with diabetes.

Because health services utilization and costs for diabetes care may be influenced by various factors, including patient demographic and clinical characteristics (particularly the disease severity defined by the presence/absence of specific chronic conditions), it is appropriate to examine costs at the patient-level. The cost drivers associated with diabetes care and the underlying cost distributions must be better understood in order to specifically target the chronic conditions that involve the greatest economic costs. These estimates may aid in economic evaluations of emerging therapies aimed at preventing or identifying the targeted complications and help develop the appropriate health care strategies.

Recent studies conducted in the United States used multivariate regression analysis in an attempt to generate standardized predictions and estimate variation in costs of diabetes care after adjustment for various factors. While the multivariate cost formulations reported in these studies described the probability of having higher costs in relation to presence of specific major complications, the generalization of their results to other health care organizations is limited. The cohorts were broadly representing patients with diabetes enrolled in managed-care organizations located in different geographical parts of the United States. The studies used different strategies for identifying study populations (which differed in terms of age, race, and diabetes type, duration and severity) and used different eligibility criteria. Different studies included and excluded different cost components or used different methods to calculate them. Their regression models differed in terms of the cost predictors included.

In Canada, the economic impact of diabetes is likely to be immense and, given the epidemiological trends, is also likely to increase with time. The health care system's ability to deal with the disease is still limited by the lack of recent, comprehensive, and accurate data on the economic burden of diabetes and its associated complications. This makes it difficult to make predictions as to how potentially cost-effective emerging therapies might be. However, the development of comprehensive administrative databases is likely to improve our knowledge in this area. Canadian investigators have already demonstrated the validity of identifying people with diabetes by using centralized healthcare claims data to study epidemiology and excess costs of diabetes [12, 51].

3. Methodology

This is a retrospective observational cross-sectional study designed to estimate the direct costs of health care for patients with diabetes mellitus and associated complications and comorbidities in Saskatchewan for the year 1991. The basic approach involved the identification of a cohort of patients, collection of information on all health care resources used during 1991 (those associated with insured physician and hospital services and with drugs covered by the Saskatchewan Drug Plan) and then assigning a cost to each resource used.

The main objectives of this study were to estimate the average annual direct costs of health care per patient in 1991 for patients with diabetes and to characterize some of the important cost drivers (demographics - age, sex, and race- and disease severity measured by presence or absence of and number of associated complications) using data from Saskatchewan Health.

Specific research objectives were to estimate the total costs of health care, hospital care, physician services, and total costs for outpatient prescription drugs for these patients according to presence or absence of certain diabetes-associated complications and to determine the contribution of specific complications to the estimated costs for 1991. It was hypothesized that the costs of health care for patients with diabetes vary according to the presence or absence of specific diabetes-associated complications.

Research setting and data source

Saskatchewan Health Insurance Plan provides universal health insurance for Saskatchewan residents [31, 64]. This health plan includes full coverage for most hospital and physician services (those identified as "medically necessary" services), and partial coverage for other services. Full coverage is also provided for other services depending on the service and beneficiary. The health plan maintains computerized records on all hospital admissions and physician visits for all Saskatchewan residents and on drug prescriptions only for the non-registered Indian population (referred here as general population). A basic database (Population Registry) that identifies all enrolled persons and includes population characteristics and information designating registered Indians is also maintained.

Physicians submit the information on physician services. For each physician service, the patient's identification, date of service, diagnosis (a three-digit ICD-9 code, International Classification of Diseases, 9th revision) and fee-for-service (FFS) code are entered into a physician claims database. Hospitals submit an abstract to the Canadian Institute for Health

Information (CIHI) that includes the patient's identification, dates of admission and discharge, attending physicians and CIHI provides the records back to Saskatchewan Health. These processed records include up to 16 ICD-9 diagnosis codes (three- and four-digit codes). The process for how hospital records are handled depends on the year and the hospital. Outpatient prescription drugs are also recorded according to patient ID, drug identification number (DIN), quantities dispensed, and cost. It is important to mention that the variables listed above for the physician, hospital and drug records are not the only ones collected.

Saskatchewan is one of the Canadian provinces that have created comprehensive databases to administer their single payer health care systems. The Saskatchewan databases cover the medical and pharmaceutical benefits received by practically all residents of the province [31, 64, 103]. With the exception of people whose health care is federally funded (members of the Royal Canadian Mounted Police or Canadian Forces and inmates of the federal penitentiaries), all provincial residents are eligible for health insurance coverage. Consequently, these databases provide population-based denominators. However, it is important to mention that registered Indians are not eligible for Drug Plan benefits because the federal government covers the costs of their drugs.

Another advantage is the possibility of linking the data with hospital chart and discharge summaries. The hospital separations constitute the hospital services file, the physician claims constitute the physician services file and drug plan records constitute the prescription drug file. All data can be linked via an unique personal health identification number (the registry number obtained from the Population Registry), which is included with each physician claim record, each hospital separation record, and each drug plan record.

Four administrative databases were used to create these diabetes datasets (de-identified study files) assembled by the Epidemiology, Research and Evaluation Unit of the Population Health Branch of Saskatchewan Health:

1. The Saskatchewan physician services database which includes diagnoses and procedures for each service provided;
2. the Saskatchewan hospital discharge database which includes patient diagnoses and procedures for each hospitalization;
3. the Saskatchewan drug database, which includes data on outpatient prescription drugs covered by the Drug Plan (It does not include drugs received by registered Indians); and
4. the Population Registry, which contains information about age, gender, registered Indian people status, region, etc.

The population from which the individuals in the diabetes datasets were identified consists of all residents in the province who were eligible for Saskatchewan Health coverage at any point

between January 1st 1991 and December 31st 1996. Residents were considered to have diagnosed diabetes if they had one or more outpatient prescriptions for diabetes drugs (insulin and/or oral antidiabetic agent), two or more separate physician visits with a diagnosis of diabetes within a two-year period, and/or one or more hospitalization for diabetes during the period January 1st 1991 and December 31st 1996 [80]. Except for the drug component, this definition has been validated in another Canadian province [12].

Outpatient prescription information for registered Indians is not available in the Saskatchewan databases because the federal government covers their prescriptions. Therefore, for the purposes of this report, the definition for diabetes in the registered Indian population is two or more physician visits within a two-year period and/or one or more hospitalizations for diabetes during the period January 1st 1991 to December 31st 1996 [80].

Saskatchewan Health data only flag Status or registered Indians, which is only one of the groups included within the First Nations population. Therefore, in this study, the population referred to as the registered Indians population includes only the Status or registered Indians identified with diabetes. The registered Indians population does not include other groups within the First Nations population. Neither does it include Metis or Inuit peoples.

This diabetes datasets contain variables on demographics, clinical parameters and diagnostic information, and on resource utilization (all hospital separations, physician services, and prescription drug purchases by individual beneficiaries). A brief technical description of some variables included in the diabetes datasets obtained from Saskatchewan Health is provided in Appendix 3.

The cohort used for the present study was limited to individuals with diabetes who were eligible for Saskatchewan Health coverage from January 1st 1991 until death or the end of the observation period December 31st 1991. Patient and resource use data for the calendar year 1991 were drawn from the diabetes datasets assembled by the Epidemiology, Research and Evaluation Unit of Saskatchewan Health. Data on some patient characteristics (age, gender, race), diagnostic information and data on resource utilization were extracted and abstracted to construct a dataset for analysis. The dataset for analysis was created by arranging each selected individual's record into a summary record, using the unique identifier to link all physician, hospital, and outpatient prescription drug claims.

All analyses were conducted using de-identified data.

Definition and identification of specific complication categories

Patients with specific complications were identified using computerized inpatient and outpatient ICD–9 coded diagnoses and FFS codes for the services provided by physicians as coded in the payment schedule for physician's services [81]. In the hospital services file data were grouped in eleven diagnostic categories using three-and four-digit ICD-9 diagnosis codes. In the physician services file data were grouped in eleven diagnostic categories (using three-digit IDC-9 codes) and 15 FFS categories (using FFS codes). These categories and their coded variable names are summarized in Table 3.1:

Table 3.1: Diagnostic and procedure categories

Hospital diagnostic category (coded variable name)	**Physician diagnostic category** (coded variable name)	**Procedure categories** (coded variable name)
Cardiovascular complications: Artery (hoscat1)	Cardiovascular complications: Artery (docdx01)	Vascular reconstruction procedures (docfs01)
Cardiovascular complications: Heart (hoscat2)	Cardiovascular complications: Heart (docdx02)	Amputation – toes (docfs02)
Cardiovascular complications: Vein (hoscat3)	Cardiovascular complications: Vein (docdx03)	Amputation – foot (docfs03)
Endocrine/Metabolic complications (hoscat4)	Endocrine/Metabolic complications (docdx04)	Amputation - below knee (docfs04)
Neurologic complications (hoscat5)	Neurologic complications (docdx05)	Amputation - above knee (docfs05)
Ophthalmic complications (hoscat6)	Ophthalmic complications (docdx06)	Cardiovascular surgery -CABG (docfs06)
Renal complications (hoscat7)	Renal complications (docdx07)	Cardiovascular surgery – angioplasty (docfs07)
Diabetes (hoscat8)	Diabetes (docdx08)	Transplant – renal (docfs08)
Other disorders of pancreatic internal secretion (hoscat9)	Other disorders of pancreatic internal secretion (docdx09)	Eye procedures – laser (docfs09)
Other complications (hoscat10)	Other complications (docdx10)	Eye procedures – cataract (docfs10)
Cardiovascular complications: Stroke (hoscat11)	Cardiovascular complications: Stroke (docdx11)	Dialysis – hemo – initiation (docfs11)
		Dialysis - hemo -weekly ongoing (docfs12)
		Dialysis - peritoneal -weekly ongoing (docfs13)
		Dialysis - hemo - general surgical preparation (docfs14)
		Dialysis - peritoneal - general surgical preparation (docfs15)

Using hospital and physician data, a decision algorithm was developed to identify complications for four major complication groups that have been considered as incorporating diabetes-associated complications. A list of the four major complication groups, their identifiers and the accompanying ICD-9 and FFS codes used for groupings are presented in Table 3.2:

Table 3.2: Decision algorithm for complication grouping

Group name	Description
Renal complications **(R)**	**Hospital ICD-9 codes:** 250.3; 580-588; 590; 593; 595; 596; 599.0; 791 (renal complications)
	Physician ICD-9 codes: 580-588; 590; 593; 595; 596; Z64; 791 (renal complications)
	FFS codes: 303R-308R (renal implantation); 121D-124D, 128D-132D (haemodialysis and peritoneal dialysis)
Neurologic complications **(N)**	**Hospital ICD-9 codes:** 250.5; 337.1; 354; 355; 356.8; 357.2; 358.1 (neurologic complications)
	Physician ICD-9 codes: 354; 355 (neurologic complications)
	FFS codes: 774M (amputation-toe); 770M-772M (amputation-foot); 761M-763M; 765M; 766M; 768M; 769M (amputation below- and above-knee)
Cardio-vascular complications **(C)**	**Hospital ICD-9 codes:** 401-405; 440-444; 447; 458; 459; 707; 785.4 (cardiovascular complications: artery); 250.6; 410-414; 425-428; 429.1; 429.2; 429.3 (cardiovascular complications: heart); 451-454 (cardiovascular complications: vein); 430-438 (cardiovascular complications: stroke)
	Physician ICD-9 codes: 401-405; 440-444; 447; 458; 459; 707 (cardiovascular complications: artery); 410-414; 425-429 (cardiovascular complications: heart); 451-454 (cardiovascular complications: vein); 430-438 (cardiovascular complications: stroke)
	FFS codes: 568L; 668L; 768L; 168L-170L; 460L-467L; 188L-191L; 790L; 791L (vascular reconstruction procedures); 153L-155L; 171L; 172L; 654L; 769L; 770L (cardiovascular surgery-CABG); 328A; 329A; 332A-335A; 485A; 487A; 490A; 491A (cardiovascular surgery-angioplasty)
Ophthalmic complications **(O)**	**Hospital ICD-9 codes:** 250.4; 362; 364.4; 365; 366; 377 (ophthalmic complications)
	Physician ICD-9 codes: 362; 365; 366; 377 (ophthalmic complications)
	FFS codes: 169S; 175S-178S; 251S; 269S; 369S; 493S-496S (eye procedures-laser); 135S-140S; 189S (eye procedures-cataract)
No complications **(NoComp)**	None of the above mentioned codes

In defining the groups of diabetes-related complications we included both conditions specific to diabetes (nephropathy, neuropathy, retinopathy) and conditions strongly associated with diabetes (such as cerebrovascular disease, peripheral vascular disease, amputations, ischemic heart disease, and congestive heart failure). They were selected based on the review of the clinical literature and verified by clinical consultation. Information based on claims data was used to account for severity of diabetes using diagnoses of diabetes-associated complications as a measure (presence of specific diagnoses on a claim).

This decision algorithm was used to create mutually exclusive complication groups for all study patients. Each patient was coded according to whether he/she had one or more complications in the major complication groups. A person with only one complication was coded as **R** (renopathy or renal complications), **N** (neurologic complications, including neuropathy and amputations), **C** (cardiovascular complications, including cerebrovascular disease, peripheral vascular disease, ischemic heart disease, and congestive heart failure) or **O** (ophthalmic complications or retinopathy). Persons with two or more complications were coded as **RN**, **RC**, **RO**, **NC**, **NO**, **CO**, **RNC**, **RNO**, **RCO**, **NCO**, or **RNCO** according to which group they fell into. If a case had no complications from the major groups, it was coded as **NoComp**.

The specified complications were considered to exist for a patient **if** there was one or more entries recorded for the above listed categories with a corresponding ICD-9 or FFS code at any time during the study period. For example, a patient had to have at least an entry for"hoscat6" OR for "docdx07" OR for "docfs09" OR for "docfs10", and no paid claim for any other major complication group to be in the ophthalmic complications group (O). A patient who had no paid claims for any of the diagnostic and procedure categories listed in Table 3.2 was included in the "no complication" group (NoComp). That is, the patient was coded as having no complications **if** none of the diagnostic or FFS codes for any of the diagnostic and procedure categories listed in Table 3.2 was present in his/her record from the dataset created for analysis.

Two of the procedure categories (docfs14 and docfs15) were not included in the decision algorithm since their accompanying FFS codes did not appear at any time in the dataset created for analysis.

Costing methodology

The data collected on direct costs of health care services were grouped into three categories: costs of hospital services (hospital costs), costs of physician services (doctor costs), and costs of outpatient prescription drugs (drug costs). Cost per person was calculated as the

sum of all doctor, hospital, and prescription drug 1991 costs (for general population only), whether diabetes related or not (all expressed in 1991 Canadian dollars). The units for all patient-specific resources were obtained from the diabetes datasets.

The hospital costs were based on a per diem estimate of total cost divided by total days of hospitalization. A unit cost of $500 (Canadian dollars) per day was applied [78]. The hospital cost included only those costs funded by Saskatchewan Health. Inpatient costs included all inpatient costs and services, such as drugs, laboratory tests, nursing time, and overhead costs.

Costs of physician services were based on provincial fees [81] and obtained from the actual records in physician services file (where cost was a variable for each record). Costs of drug therapy were obtained from the actual records in the prescription drug file. These were the total costs for prescription drugs, including the pharmacist fee [82]. Information on the outpatient prescription drug use by registered Indians was not recorded in the drug file and could not be estimated for this population.

Costs were assessed from the modified societal perspective, and included patient's share of costs and payer's cost (government cost).

Statistical analysis

Costs were obtained by aggregating all cost data per person. The initial analysis of the data included descriptive statistics of the costs for each category.

The literature review of research on costs of diabetes revealed that the direct costs of health care for patients with diabetes are determined by at least two major factors: disease severity (presence of and number of associated complications and comorbidities) and demographics such as age, gender, and race. Based on these considerations, models of direct costs of health care were defined using the multiple linear regression method. These models were used to estimate the determinants of costs of health care for the cases included in the study and examine the factors that were associated with the estimated costs. They were also used to predict the variation in the average total costs according to the presence and number of the complications, after adjustment for age, sex, and race.

Multiple linear regression is a statistical method used to estimate the value of one variable from values of several related predictors (explanatory variables). It predicts a single dependent variable from a set of a multiple independent variables and it has been used to provide probability and cost estimates for patients with diabetes at the individual level. Ordinary least squares (OLS), the most common method of estimating the parameters of the

multiple linear regression model, was used to determine the association between the set of independent variables considered and the costs of care [48, 53].

We included doctor costs, hospital costs, and drug costs (only for non-registered Indian individuals). The set of independent variables included patient demographic characteristics (age, sex, race) and disease severity (measured by presence and number of specific complication groups). Descriptive statistics of the resource units for each category were calculated for the dependent variable and the independent variables.

Because distribution of cost data was right-skewed, the variable "TotalCosts" was transformed using the natural logarithm method [53, 63]. The logarithmic transformation was used to adequately normalize the distribution of the cost data and to ensure more equal variances so that the regression assumptions were met. Therefore "LnTotalCosts" became the dependent variable for the regression analysis.

SPSS (Statistical Package for Social Sciences) for Windows version 10.0 (SPSS Inc., Chicago, IL) on an IBM-compatible personal computer in a Microsoft Windows 2000 environment was used for all statistical analyses. All the statistical tests that we report are two-sided. The chosen level of significance was set at <0.05 (the term statistically significant implies $p<0.05$).

OLS regression models

OLS regression analysis of total annual costs at patient level for the year 1991 for study patients with costs greater than zero was employed. The OLS regression model used in this study was as follows:

$$\text{Ln (TotalCost)} = \alpha + \beta_1 (\text{age}) + \beta_2 (\text{sex}) + \beta_3 (\text{race}) + \beta_4 \text{Comp}_R + \beta_5 \text{Comp}_N + \beta_6 \text{Comp}_C + \beta_7 \text{Comp}_O + \beta_8 \text{Comp}_{RN} + \beta_9 \text{Comp}_{RC} + \beta_{10} \text{Comp}_{RO} + \beta_{11} \text{Comp}_{NC} + \beta_{12} \text{Comp}_{NO} + \beta_{13} \text{Comp}_{CO} + \beta_{14} \text{Comp}_{RNC} + \beta_{15} \text{Comp}_{RNO} + \beta_{16} \text{Comp}_{RCO} + \beta_{17} \text{Comp}_{NCO} + \beta_{18} \text{Comp}_{RNCO} + \varepsilon$$

In this model:

1. **Ln (TotalCost)** is the natural logarithm of direct costs for health care of treating diabetes and commonly associated complications per patient in 1991. Total Cost included medical, hospital, and (for general population only) drug costs.
   - **Age** is a continuous variable, calculated by different years between 1991 and recipient year of birth.
   - **Sex** is a binary variable, in the electronic diabetes dataset (defined as males=0; females=1).

- **Race** is a binary variable, which classified patients as registered Indians (race=1) representing the registered Indians population and non-registered Indians (race =0) representing the general population in the dataset for analysis.
- **$Comp_R$** ... **$Comp_{RNCO}$** are 15 binary variables, defined as follows
  - **$Comp_R$** = patients identified with **renal complications only** [yes=1, no=0],
  - **$Comp_N$** = patients identified with **neurologic complications only** [yes=1, no=0],
  - **$Comp_C$** = patients identified with **cardiovascular complications (artery, vein, heart) only** [yes=1, no=0],
  - **$Comp_O$** = patients identified with **ophthalmic complications only** [yes=1, no=0],
  - **$Comp_{RN}$** = patients identified with **renal and neurological complications only** [yes=1, no=0],
  - **$Comp_{RC}$** = patients identified with **renal and cardiovascular complications only** [yes=1, no=0],
  - **$Comp_{RO}$** = patients identified with **renal and ophthalmic complications only** [yes=1, no=0],
  - **$Comp_{NC}$** = patients identified with **neurologic and cardiovascular complications only** [yes=1, no=0],
  - **$Comp_{NO}$** = patients identified with **neurologic and ophthalmic complications only** [yes=1, no=0],
  - **$Comp_{CO}$** = patients identified with **cardiovascular and ophthalmic complications only** [yes=1, no=0],
  - **$Comp_{RNC}$** = patients identified with **renal, neurologic and cardiovascular complications only** [yes=1, no=0],
  - **$Comp_{RNO}$** = patients identified with **renal, neurologic and ophthalmic complications only** [yes=1, no=0],
  - **$Comp_{RCO}$** = patients identified with **renal, cardiovascular and ophthalmic complications only** [yes=1, no=0],
  - **$Comp_{NCO}$** = patients identified with **neurologic, cardiovascular and ophthalmic complications only** [yes=1, no=0], and
  - **$Comp_{RNCO}$** = patients identified with **all four complications** [yes=1, no=0].
- α is the intercept (constant)
- β_1 - β_{18} are regression slope coefficients
- ε is the error term.

Because complete cost data was not available for all individuals (drug data is not available for registered Indians with diabetes), separate OLS regression models were created for total annual costs of health care:

1. The first model (Model 1) regressed total annual costs (including hospital costs and doctor costs only) for the year 1991 per study patient (with costs greater than zero) on age, sex, race, and disease severity defined by presence/absence or the specific complications (using data for all study patients).
2. The second model (Model 2) regressed total annual costs (including hospital costs, doctor costs, and drug costs) for the year 1991 per non-registered Indian patient (with costs greater than zero) on age, sex, and disease severity defined by presence/absence or the specific complications (using data for all non-registered Indians patients).

Two-part regression models are often used when a significant percentage of patients incur zero costs over the period of observation [63]. A two-part model directly addresses the problem of zero-cost observations (which exacerbates the asymmetry of cost data distribution) by combining two separate models: a logistic regression to predict whether cost with be zero and a linear regression for non-zero costs. Because the proportion of patients with zero costs was small in both study cohort and the sub-cohort of non-registered Indian patients (1.32% and 0.02%, respectively), the two-part model was converted to a one-part model by adding $1 to those patients with zero costs.

Among the complication terms, the variable representing patients with "no complications" in 1991 was taken as the reference variable. This was done to avoid colinearity among complication variables which makes parameter estimates imprecise (high variance) and hypothesis testing considerably less powerful. Thus, estimated regression coefficients associated with the specified variables should be interpreted with respect to this reference variable in the respective groups. For example: if the coefficient estimate associated with one complication variable is significant (at α=0.05) and positive, we could say that study patients suffering from the complication(s) considered incur significantly higher costs for health care services needed to treat diabetes and associated complication than do patients with no complication(s).

Interpretation

To determine cost estimates for specific cases we first assigned certain values for the independent variables included in each model. Then we calculated the value for the Ln(TotalCost), which we then transformed back to obtain the cost estimate. For example, to estimate the average annual costs incurred by a male, non-registered Indian patient, aged 45 years, with none of the considered major complications, we first assigned the following

values: race=0; age=45; sex=0; $Comp_R$ =0; and $Comp_{RNCO}$ =0. Then we calculated the mean costs on the logarithmic scale. To derive estimates of mean costs on the original scale, the logarithmic means were then transformed back to a dollar scale using exponential function.

The R^2 statistic from the regression model represents the proportion of individual level variation explained by the independent variables in the model. In this study, R^2 statistic measures the ability of explanatory variables in the model to account for differences in expenditures among study patients. The higher R^2 statistic the higher the proportion of variation among individuals is explained by the model.

Disclaimer:

"This Study is based in part on de-identified data provided by the Saskatchewan Department of Health. The Interpretation and conclusions contained herein do not necessarily represent those of the Government of Saskatchewan or the Saskatchewan Department of Health".

4. Results

Patient characteristics

The study cohort consisted of 25,961 patients representing all individuals who met the study definition for diagnosed diabetes (registered Indians and non-registered Indians, males and females, all ages, both type 1 and type 2 diabetes) eligible for health care coverage in Saskatchewan for calendar year 1991. A summary of the distribution of patient demographic characteristics obtained from the integrated claims data used in this study is presented in Table 4.1:

Table 4.1: Demographic characteristics of the study population

Demographic characteristics	Description
Age	
• Range	• 0-80 years
• Mean (Standard Deviation)	• 61.70 (16.35)
• Distribution by age-group (%)	
➢ <18 years	• 430 (1.66%)
➢ 18-44 years	• 3,620 (13.94%)
➢ 45-64 years	• 8,358 (32.20%)
➢ ≥65 years	• 13,553 (52.20%)
Sex (%)	
• male	• 13,499 (52%)
• female	• 12,462 (48%)
Race (%)	
• general population (non-registered Indians)	• 23,967 (92.32%)
• registered Indians population (registered Indians)	• 1,994 (7.68%)

In this cohort, 84% were adults aged ≥45 years and their mean age was 67.20 years (Standard Deviation 10.23). Of these patients, 52 % were men and 47.6% were women. The mean age for children and adolescents (aged< 18 years) was 11.85 years (Standard Deviation 4.00). Of all patients, 23,967 were classified as non-registered Indians (race=0) and represented the general population and 1,994 were registered Indians (race=1) who represented the registered Indians population.

The general population was more heavily distributed in the older age categories than was the registered Indians population. Of all non-registered Indians 20,517 patients (85.61%) were 45

years of age and older (mean age of 67.75, Standard Deviation 10.05) and 13,151 (54.87%) were aged ≥65 years (mean age of 74.13 years, Standard Deviation 5.13). In these age categories, 53.2% and 49.7% of non-registered Indians were men. In the registered Indians population 1,394 patients (69.91%) were 45 years of age and older and 402 (20.16%) were aged ≥65 years (mean age of 71.04 years, Standard Deviation 5.11). For the registered Indians population, women represented the majority in both old age groups, (59.5% and 60.9%, respectively).

The frequencies of major complication groups and any of their combinations for the patients in the study cohort and for the patients in the sub-cohorts representing the registered Indians and general populations are summarized in Table 4.2:

Table 4.2: Frequency of specific complications and their combinations

Complication groups	All study patients	Non-registered Indians	Registered Indians
R	616 (2.4%)	480 (2.0%)	136 (6.8%)
N	221 (0.9%)	197 (0.8%)	24 (1.2%)
C	8,285 (31.9%)	7,808 (32.6%)	477 (23.9%)
O	2,123 (8.2%)	2,038 (8.5%)	85 (4.3%)
RN	15 (0.1%)	11 (0.0%)	4 (0.2%)
RC	963 (3.7%)	858 (3.6%)	105 (5.3%)
RO	169 (0.7%)	145 (0.6%)	24 (1.2%)
NC	249 (1.0%)	227 (0.9%)	22 (1.1%)
NO	61 (0.2%)	56 (0.2%)	5 (0.3%)
CO	2,386 (9.2%)	2,293 (9.6%)	93 (4.7%)
RNC	44 (0.2%)	37 (0.2%)	7 (0.4%)
RNO	17 (0.1%)	14 (0.1%)	3 (0.2%)
RCO	385 (1.5%)	352 (1.5%)	33 (1.7%)
NCO	142 (0.5%)	125 (0.5%)	17 (0.9%)
RNCO	45 (0.2%)	41 (0.2%)	4 (0.2%)
NoComp	10,240 (39.4%)	9,285 (38.7%)	955 (47.9%)

As shown in Table 4.2 and in Table 4.3, for the majority of patients with one or more complications, only one complication was present and cardiovascular complications were the

most common. Only small percentages of patients in the study cohort or in registered Indians and general populations had complications from three or more complication groups.

Table 4.3: Distribution of major complications

Number of major Complications present	All study patients (n=25,961)	Non-registered Indians (n=23,967)	Registered Indians (n=1,994)
No complications	10,240 (39.4%)	9,285 (38.7%)	955 (47.9%)
One complication	11,245 (43.3%)	10,523 (43.9%)	722 (36.2)
Two complications	3,843 (14.8%)	3,590 (15.0%)	253 (12.7%)
Three complications	588 (2.3%)	528 (2.2%)	60 (3.0%)
Four complications	45 (0.2%)	41 (0.2)	4 (0.2)

Costs of diabetes care

The estimated total direct cost of diabetes care for the study cohort consisting of 25,961 patients eligible for health coverage in Saskatchewan in 1991 was $101,721,994 (Canadian dollars). Because there were no drug cost data for the patients in the registered Indians population, total costs included only hospital costs and doctor costs. The costs for hospital care ($84,594,000) accounted for 83% of the total amount. The costs for physician visits accounted for the reminder of 17% ($17,127,994).

Table 4.4: Costs of direct health care for all study patients

Costs	Sum	Mean	Standard Deviation (SD)
Total costs	101,721,994.24	3,918.26	9,579.15
Hospital costs	84,594,000.00	3,258.50	9,102.05
Doctor costs	17,127,994.24	659.76	835.49

For the registered Indians population, consisting of 1,994 patients, the estimated total direct cost of diabetes care in 1991 was $8,936,024 (see Table 4.5). Total costs included only hospital costs and doctor costs. The costs for hospital care ($7,488,000.00) accounted for 84% of the total amount. The doctor costs accounted for the reminder of 16% ($1,448,024).

Table 4.5: Costs of direct health care for all registered Indians

Costs	Sum	Mean	Standard Deviation (SD)
Total costs	8,936,023.82	4,481.46	9,240.08
Hospital costs	7,488,000.00	3,755.27	8,755.75
Doctor costs	1,448,023.82	726.19	805.02

The total direct health care costs incurred in 1991 by all 23,967 patients representing the general population was estimated at $111,402,817 (see Table 4.6). For this sub-cohort, total costs included hospital cost, doctor costs, and drug costs. Hospital care ($77,106,000) accounted for 69% of the total amount. Drug costs were the second highest component at 17% ($18,616,847). Physician visits accounted for 14% ($15,679,970).

Table 4.6: Costs of direct health care for all non-registered Indians

Costs	Sum	Mean	Standard Deviation (SD)
Total costs	111,402,816.98	4,648.18	9,732.97
Hospital costs	77,106,000.00	3,217.17	9,129.22
Doctor costs	15,679,970.42	654.23	837.75
Drug costs	18,616,846.56	776.77	824.11

Table 4.7 summarizes the average costs per complication group for registered Indians and non-registered Indians who incurred costs. Although values showed are averages, certain complication groups had small numbers of patients and the data should be interpreted carefully. Thus, among the non-registered Indians, the highest costs were for 37 patients (mean age of 68.4 years; range 28-80 years) in the RNC group (suffering from renal, neurologic, and cardiovascular complications). The second highest total costs were incurred by 41 patients (mean age of 66.9 years; range 36-80 years) in the RNCO group, with conditions related to all four major complication groups (Table 4.7). Among registered Indians, the highest total costs were incurred by seven cases (mean age of 59.1 years, range 41-70 years) affected by a combination of renal, neurologic, and cardiovascular complications (Table 4.7). The second highest costs were incurred by 17 registered Indians (mean age 55.9 years, range 34-80 years) suffering from a combination of neurologic, cardiovascular, and ophthalmic complications (in the NCO group).

Table 4.7: Average costs per complication group for patients who incurred costs

Group	Non-registered Indians (n=23,967)				Registered Indians (n=1,994)		
	Hospital cost (SD)	*Doctor cost (SD)*	*Drug cost (SD)*	*Total cost[a] (SD)*	*Hospital cost (SD)*	*Doctor cost (SD)*	*Total cost[a] (SD)*
R	5296 (11400)	796 (775)	861 (1148)	6092 (11783)	3309 (4678)	802 (722)	4111 (5080)
N	2439 (5852)	841 (670)	669 (671)	3280 (6262)	4313 (8141)	901 (790)	5213 (8843)
C	3934 (9736)	682 (795)	873 (809)	4616 (10168)	4075 (7579)	772 (829)	4848 (8068)
O	952 (3409)	592 (512)	729 (643)	1544 (3631)	2571 (5468)	644 (418)	3215 (5721)
RN	2227 (4936)	761 (649)	1573 (2994)	2989 (95327)	7125 (4366)	785 (343)	7910 (4606)
RC	11858 (17433)	1299 (1382)	1124 (1172)	13158 (18025)	11081 (17374)	1398 (1351)	12479 (18118)
RO	3790 (7771)	1029 (936)	1389 (1849)	4818 (8324)	8271 (13142)	1300 (1003)	9571 (13507)
NC	11652 (18408)	1406 (1445)	1063 (1083)	13058 (19118)	11409 (11088)	1406 (943)	12815 (11110)
NO	3911 (11036)	1096 (836)	837 (858)	5007 (11432)	9000 (4077)	1582 (789)	10582 (4762)
CO	4229 (8878)	1039 (939)	1101 (903)	5268 (9402)	6349 (11369)	1189 (746)	7538 (11823)
RNC	27757 (27005)	3264 (3319)	1830 (2323)	31021 (28030)	25214 (27045)	1571 (1134)	26785 (28011)
RNO	11786 (13230)	3294 (2677)	1598 (1339)	15080 (14949)	4333 (6658)	986 (532)	5320 (6501)
RCO	12145 (178162)	1910 (1677)	1496 (1337)	14055 (18035)	11864 (14598)	1899 (1480)	13763 (15611)
NCO	14604 (20837)	1706 (1255)	1302 (1015)	16310 (21362)	24147 (30506)	1810 (851)	25957 (30817)
RNCO	26073 (31637)	3025 (2209)	2029 (2246)	29098 (33014)	12125 (9681)	1997 (1497)	14122 (10955)
NoComp	1051 (19)	796 (775)	530 (578)	1416 (4570)	1524 (4109)	469 (513)	1993 (4392)

[a] estimates include hospital and doctor costs but do not include drug costs; SD – standard deviation

The graphical representations of these average costs are showed in Figure 4.1 and Figure 4.2:

Figure 4.1: Average costs per complication group for non-registered Indians

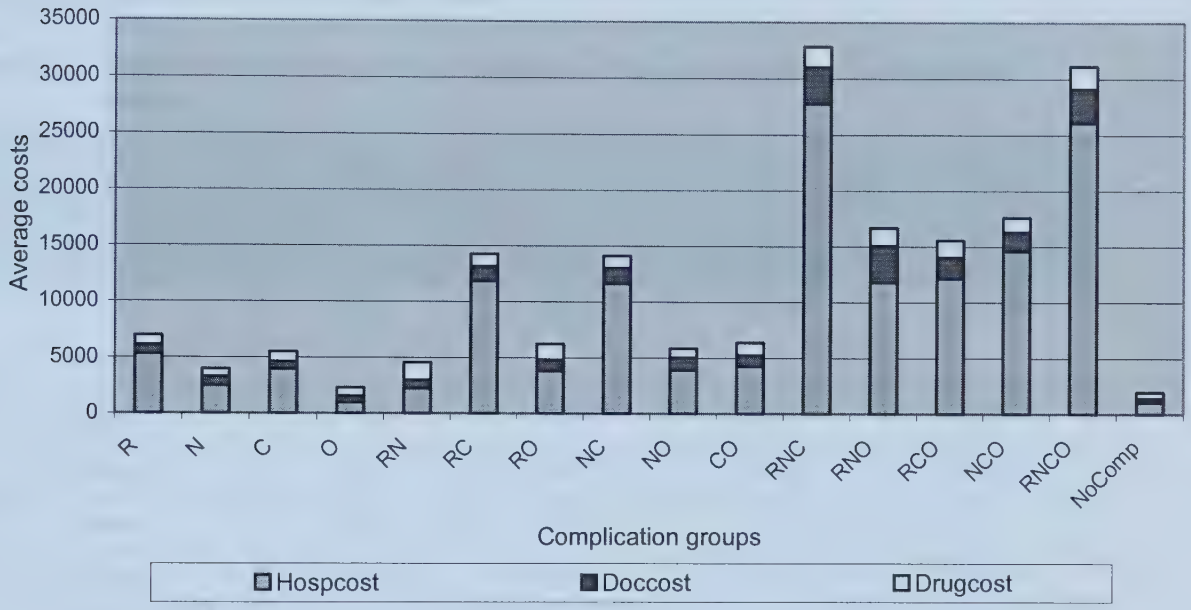
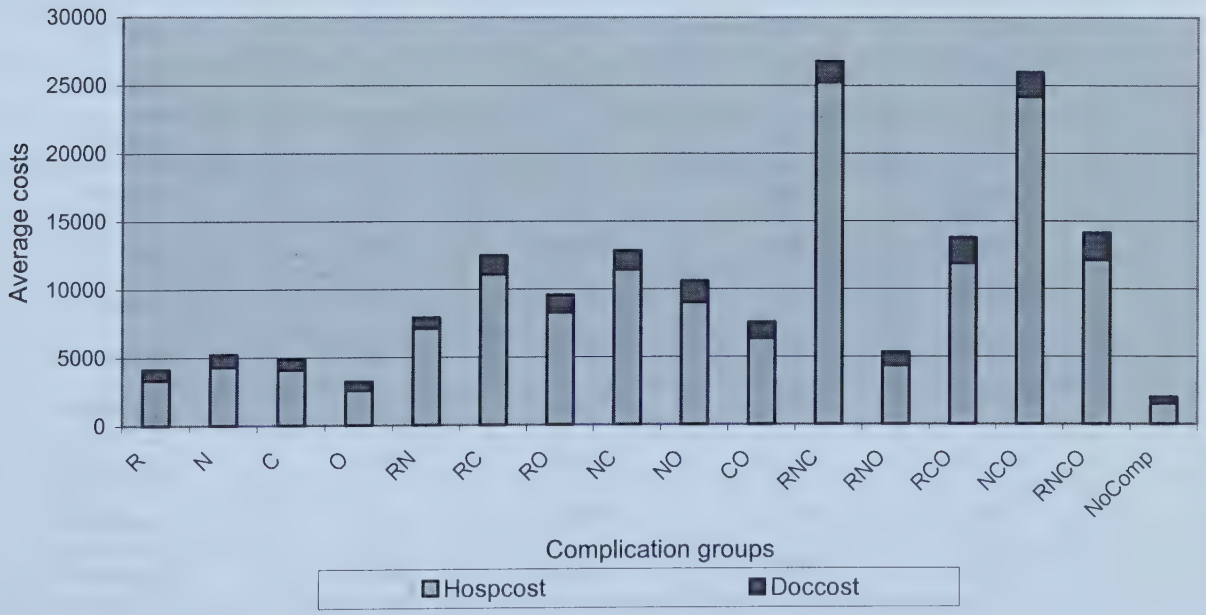


Figure 4.2: Average costs per complication group for registered Indians



Regression analyses of total costs

Table 4.8 presents the summary of multiple regression analyses conducted to assess the relationship between the total costs of diabetes care per patient for the year 1991 and the predictor variables considered for each model.

Table 4.8: Coefficient and t-test values estimated from regression models on total costs

Independent variable	Model 1 (R^2 = 0.226)		Model 2 (R^2 = 0.238)	
	Coefficient	t-test	Coefficient	t-test
Const	5.083	116.258**	6.468	198.078**
Age	0.008	11.204**	0.003	4.828**
Sex	0.170	7.957**	0.143	8.918**
Race	0.611	15.077**	--	--
$Comp_R$	1.720	24.225**	1.278	22.032**
$Comp_N$	1.414	12.214**	0.889	9.985**
$Comp_C$	1.224	46.193**	0.995	49.748**
$Comp_O$	0.719	17.603**	0.495	16.263**
$Comp_{RN}$	1.478	3.359**	0.814	2.183*
$Comp_{RC}$	2.689	46.100**	2.134	47.586**
$Comp_{RO}$	1.846	13.967**	1.437	13.873**
$Comp_{NC}$	2.735	24.998**	2.065	24.815**
$Comp_{NO}$	1.980	9.059**	1.295	7.815**
$Comp_{CO}$	1.746	43.528**	1.372	45.942**
$Comp_{RNC}$	3.947	15.339**	3.244	15.918**
$Comp_{RNO}$	3.135	7.586**	2.577	7.791**
$Comp_{RCO}$	2.954	33.224**	2.318	34.313**
$Comp_{NCO}$	3.158	21.914**	2.418	21.681**
$Comp_{RNCO}$	3.959	15.561**	3.201	16.534**

** $p \leq 0.001$; * $p < 0.05$

Because drug cost data was not available for the registered Indian population, separate OLS regression models were created for average total costs of diabetes care for 1991. Model 1 regressed the natural logarithm of total costs (including hospital costs and doctor costs only) per study patient on age, sex, race, and disease severity (using data on all 25,961 study patients). Model 2 regressed the natural logarithm of total costs (including hospital costs, doctor costs, and drug costs) per non-registered Indian patient on age, sex, and disease severity (using data on all 23,967 non-native patients).

Model 1 explained 22.6% of the variance in the average natural logarithm of the annual total direct costs for the study cohort (F=421.303). All independent variables included were positively associated with the direct costs of diabetes care per study patient, at $p \leq 0.001$. These results indicate that age, sex, race, and severity of diabetes as defined by presence/absence of specific complications are all significant predictors of costs of diabetes care (i.e., as age increased, costs increased and when specific complications or any of their combinations were present costs also increased). For example, the average annual cost of care for a non-registered Indian patient (male, aged 45 years) with none of the specified complications was estimated to be $230. The average annual costs for a registered Indian patient (male, aged 45 years) with none of the specified complications was estimated to be $424.

Among the disease severity variables, both $Comp_{RNCO}$ (presence of all complications) and $Comp_{RNC}$ (presence of renal, neurologic, and cardiovascular complications only) maximized the costs of health care, holding the other variables constant. For example, the average annual cost of care for a non-registered Indian patient who would be comparable to the one described above (male, aged 45 years) suffering from all specified complications was estimated to be $12,047. Similarly, the costs for a non-registered Indian (male, aged 45 years), suffering from renal, neurologic, and cardiovascular complications was estimated to be $11,907. Presence of neurologic, cardiovascular, and ophthalmic complications ($Comp_{NCO}$) and presence of renal, neurologic, and ophthalmic complications ($Comp_{RNO}$) also led to substantial cost increases in the study cohort.

Similarly, in Model 2 all independent variables considered were positively associated with the direct costs of health care for non-registered Indian patients with diabetes and specified complications, at $p<0.05$. This model explained 23.8 % of the variance in the average natural logarithm of the total annual direct costs for the non-registered Indian patients studied (F=439.547). Presence of renal, neurologic, and cardiovascular complications ($Comp_{RNC}$) and presence of all specific complications ($Comp_{RNCO}$) had the highest impact on the total annual costs (holding the other variables constant). Presence of renal, neurologic, and

ophthalmic complications ($Comp_{RNO}$) and presence of neurologic, cardiovascular, and ophthalmic complications ($Comp_{NCO}$) also were associated with high cost coefficients.

Interaction terms

Because we wanted to keep the models as simple as possible they did not include interaction terms. However, observing the differences in the distribution of complications in the registered and non-registered Indians populations, we were interested in the association between race and disease severity variables and how it impacts on the annual cost of care per study patient. Therefore we ran regression Model 1 after we included five interaction terms between race and some severity variables ($Comp_C$, $Comp_{CO}$, $Comp_O$, $Comp_R$, and $Comp_{RC}$). We chose these disease severity variables because they represented the groups with the most frequent complications in the study cohort.

Regression results showed that all coefficients for the interaction terms were different from zero and negative but only three were statistically significant at $p<0.05$ (those representing the interaction between race and $Comp_C$, race and $Comp_R$, and race and $Comp_{RC}$). The coefficients for the other independent variables (age, sex, race, and all disease severity variables) remained significant and positive and their values changed slightly. The value of R^2 increased to 0.227 from 0.226 (which is the R^2 value for Model 1 without the interaction terms).

These results suggest that there is interaction between race and presence of cardiovascular complication, race and presence of renal complications, and race and presence of both renal and cardiovascular complications. We need to keep these terms in Model 1 and explain the results by mentioning all variables since they are all important significant determinants of cost of care and dependent on each other.

The interaction terms were negatively associated with the average annual cost suggesting that being registered Indian affected by cardiovascular complications only, or by renal complications only, or by a combination of renal and cardiovascular complications, is associated with a decrease in costs of care.

5. Discussion

To our knowledge, the present study is the first attempt to estimate annual direct costs of health care for diabetes and associated complications at the patient level in Canada, and among the few reported elsewhere. Using 1991 data from the Saskatchewan Health's linkable administrative databases we estimated the overall costs of diabetes care according to presence/absence of single and multiple major complications associated with diabetes.

The annual cost of care for the study cohort (including only hospital costs and costs associated with physician visits) was over $100 million, with hospitalization accounting for 83% of this amount. The mean annual cost was $3,918 per study patient. However, the estimated costs showed large inter-individual variation. Our study also intended to characterize a range of demographic and clinical factors that might explain this variation and be predictive of higher costs among patients with diabetes.

Results of the regression analyses confirmed what might have been expected based on the reviewed evidence from the published literature on diabetes and its clinical and economic burdens. That is, known predictors of morbidity and mortality associated with diabetes also tend to determine utilization and costs of health care services. Each of the disease severity variables had a significant positive association with overall costs, and all complication groups were significantly different from the "no complication" group. Cost per person was lowest in the "no-complication" group and highest in the RNC, NCO, and RNCO groups.

Our findings showed that as the number of comorbid complications increased, the cost per person increased. These results make sense. It would be assumed that patients with more severe diabetes would require more and more specialized health care services and would incur higher costs than those patients with diabetes but without any of the specified complications. Also, these results are consistent with findings from the published literature reviewed. They confirm the importance of diabetes severity in determining costs, indicating that the number of complications present significantly accounted for the increase in the direct costs of health care.

Most of the cost prediction studies reviewed also reported a statistically significantly positive association between costs/charges and disease severity as measured by presence/absence of specific diabetes associated complications and/or comorbidities [10, 15, 37, 42]. These studies found that costs/charges increased with higher disease severity and that, particularly, the presence of cardiovascular disease and/or the presence of renal disease were associated with significantly higher costs/charges for care of patients with diabetes.

Each of the demographic variables considered as predictors in the present study had a statistically significant positive association with the overall costs of diabetes care. Older patients had higher overall costs, confirming the expectation that as patients with diabetes age, the disease would become more severe and they would require more health services and incur higher costs. Age was also found to be a significant predictor of higher costs of diabetes care in another three models [10, 37, 42]. Brown et al [15] reported that age was a nonsignificant predictor of costs of complications in their multivariate regression model. In the other cost prediction studies reviewed [58, 79, 101] the statistics describing the association and its significance were not available or not clearly reported.

The sex variable was statistically significant and positive, suggesting that being a woman with diabetes is associated with higher costs of health care. Brown et al [15] also found that female gender was a significant predictor of higher expenditures (controlling for age and stage of complication) in their model. However, Guo et al [42] found that male gender was a significant predictor for higher costs. Another cost prediction study reviewed found that sex was not a significant predictor [10], and for the other studies the statistics describing the association and its significance were not available or not clearly reported [37, 58, 79, 101].

Our study also found race variable to be statistically significant and positive, implying that being registered Indian was associated with higher costs for diabetes care. This result is not surprising and is consistent with findings reported recently by Jacobs et al [51]. The investigators found that Indian persons with diabetes in Manitoba incurred markedly higher per capita health care costs (including hospitalization costs and costs associated with personal home care services, professional services, and outpatient services) than persons with diabetes in the general population, with most of the excess utilization costs due to hospitalizations. They used a previously validated definition [12] to identify patients with diabetes, as we did in our study.

Among the cost prediction studies reviewed only two included race as an explanatory variable [41, 59]. In the study by Guo et al [42] race was classified as white and nonwhite (which included Black, Hispanic, Native Indian, and Asian people). The investigators found that the white race was a significant predictor of higher direct costs of illness in their model and reported that the cost for a white patient was $1330 (USD) higher than that for a nonwhite patient. Krop et al [58] included race as one of the demographic factors examined for association with increased expenditures, but did not report statistics to describe the association and its significance.

The preliminary tests conducted to study the association between race and disease severity variables and its impact on the annual cost per study patient showed unexpected results.

They suggested that because of the interaction, the presence of cardiovascular complications, of renal complications, or of a combination of renal and cardiovascular complications was associated with lower costs in registered Indians. These results cannot be immediately explained:

- We might have obtained these results because the measure of cost used did not include drug costs and clinic costs of dialysis.
- They may be a function of this study's limitations imposed by the research design as described in the next section of this chapter.
- They may also be a function of the way the study cohort was divided into the two sub-cohorts by race, with the registered Indians sub-cohort including only the individuals flagged by Saskatchewan Health as Status or registered Indians and the general population including all other residents (such as other groups of Aboriginal People, Caucasians, Hispanics, Chinese, and other ethnic groups).
- These results may say that registered Indians, when compared to non-registered Indians, die sooner after they develop these complications (alone or combined) because of their attitude towards the disease and therapy or access to health care services.

The reasons why the interaction between race and the disease severity variables considered in this study leads to a decrease in the annual average costs need further elucidation.

It is difficult to compare with any degree of accuracy our results with the results reported by the previous cost prediction studies. All studies provided an indication of multivariate prediction of total costs/charges, simultaneously controlling for numerous confounding variables in determining the predictors of costs of diabetes care at patient-level. The reported findings suggested that costs/charges of care for patients with diabetes are influenced by certain demographic and clinical factors, but showed a range of results. The differences between our findings and the results reported by these studies might reflect the differences in the methodologies employed.

Limitations and refinements

Although we described the deficiencies in the existing literature and consider that our cost estimates are more relevant to the Canadian context, the results of our study must be considered in the light of the limitations imposed by the research design. First, there are several limitations relating to identification of people with diagnosed diabetes in the study population, which may contribute to the underestimation of the reported cost data:

- The estimates were solely based on the information contained in the diabetes datasets from Saskatchewan Health. People with diabetes but with no hospitalizations for diabetes, with no outpatient prescriptions for diabetes medication, and less than two physician visits for diabetes within a two-year period during 1991-1996 were not included in this study.
- Some Indians might not have been identified as Status or registered Indians in the Saskatchewan Health Population Registry. So, they might have been excluded from the registered Indians group and included in the non-registered Indians sub-population.

Individuals with undiagnosed diabetes were excluded from this study, as they cannot be identified from the administrative databases. The reviewed literature suggested that the number of persons with undiagnosed diabetes might be as high as that of persons with diagnosed diabetes. Although people with undiagnosed diabetes may not be expected to incur health care costs as high as those with diagnosed diabetes, costs might increase over time as the associated complications necessitate more frequent and intensive health care services.

Our estimate of total direct costs of health care for patients with diabetes in Saskatchewan in 1991 understates the actual costs because we did not include all direct costs:

- Direct costs of health care arising from diabetes are the costs associated with the primary and secondary prevention, detection, treatment, rehabilitation, and long-term care. Most previous cost prediction studies concentrated on the costs associated with hospitalization, physician visits, and prescription drugs and the same approach was followed in this study.

- We excluded costs associated with outpatient surgery, which was less of a problem in 1991 than it would be today.
- The analysis did not include clinic costs of dialysis among the beneficiaries because complete information on the intensity of use of this resource was not recorded in and, therefore, not abstracted from any of the databases of Saskatchewan Health (Downey Winanne, Saskatchewan Health, personal communication – June, 1998).

- Also, costs associated with other important types of services such as nursing home care, non-prescription drugs, outpatient/ambulatory care provided by health care providers other than physicians, emergency room care, home health care, dental care, self-care equipment, and medical rehabilitation were not considered for this study. Previously published estimates suggested that total costs of care for patients with diabetes could increase considerably if these costs were included.

Our measure of costs also excluded non-medical costs such as out-of-pocket expenses for dietary recommendations and transportation to receive care and their exclusion does cause an underestimation of total costs of diabetes care. Also excluded from the analyses were indirect costs associated with diabetes and its complications such as forgone productivity due to disability and premature death or costs for lost work or wages for caretakers.

Using data from the administrative databases to examine factors associated with increased costs also has several limitations:

- The study failed to distinguish between the two main types of diabetes. Even though the two types of diabetes exhibit similar related complications, they have different etiologies and therefore different costs. Some evidence suggested that the problem associated with hospitalization of diabetic patients lies primarily with type 2 diabetes cases [6, 16, 27, 49, 50, 85].
- Only crude measures of disease were available making distinctions of severity within diagnostic categories difficult.
- Miscoding of conditions might occur.
- The data did not include information on the costs of health care services that were not covered by Saskatchewan Health in 1991.

However, despite these limitations, by using the administrative data, our cost study had the advantage to be based on real-world data from a large and broadly representative population. Also we were able to include prescription drug data in the analysis.

Certain aspects of the regression models used are also worth mentioning. They did not include interaction terms. Because the study was focused on complications from the major complications groups and their combinations, by creating the mutually exclusive combination groups we covered the interaction between the complications considered. However, the models did not include interaction terms between demographic variables and the disease severity variables considered. This might have improved the model fit by acknowledging the possible associations between different major complications and age, sex, and race. Including other important explanatory variables such as therapy (oral drugs only, insulin only, and both oral drugs and insulin), type of diabetes (type 1 and type 2 diabetes) and residence (rural vs. urban residence) could have also refined the regression analysis.

Limitations and refinements notwithstanding, the results reported by this study provide Canadian cost estimates for diabetes and associated chronic complications at a level that is functional for health care researchers and policy decision makers. This study presents evidence that costs of health care for patients with diabetes increase substantially with the

presence of one or more associated chronic complications. Complications are costly and any delay in their occurrence and/or progression may reduce costs. Efforts to delay or avoid development of cardiovascular, renal and neurologic complications, as well as vision and foot problems would be beneficial not only to the patient but also to the health care system.

Extrapolation from 1991 to present

If we were to extrapolate from 1991 to present, two scenarios might have emerged. In the first scenario, even after adjusting the direct costs of diabetes care for inflation and changes in prevalence to 2001, the cost estimates might have decreased, despite using roughly similar methods:

- Intuition suggests that the many preventive measures and the early intervention programs developed and implemented during the last decade for good diabetes control, care and management should have saved money. If we consider the recent government actions taken at the federal and provincial levels for primary and secondary prevention and the development and implementation of some cost-effective techniques for screening complicating conditions, the rate of complications could have been reduced leading to a decrease in both physician visits and hospitalization costs of diabetes care. With the introduction of the more intensive therapies and adequate control and self-management strategies that lead to improved glycemic control, costly inpatient hospitalizations might have been reduced, leading to a decrease in the estimated direct costs of diabetes care. Also the development and implementation of better diabetes education programs and improvement of access to these programs for the newer cohorts of patients might have been translated into lower probabilities of complications (especially those directly related to glycemic control and microvascular diseases) and lower per capita costs of care.
- During the last decade both hospital separations and hospital days due to diabetes and associated complications might have been decreased (leading to lower hospital costs) due to the general shift from inpatient to outpatient care in Canada's health care system. This might also reflect the understanding that the patients need to learn how to control and self-manage the disease in their normal environment, and a better understanding of patients' behavior with respect to health compliance. Also, the recent increased public and professional awareness of the risk factors and symptoms of diabetes and improved self-care might have reduced the need for hospitalization, thus lowering the associated costs.
- The increase in the health care professionals' knowledge and their ability to care for people with diabetes and the changes in the treatment practices (with the implementation of the recently issued clinical practice guidelines for the management of diabetes in

Canada) might have also led to lower probabilities of complications and in the end to lower costs of diabetes care.

On the other hand, the costs of diabetes care might have been higher these days and several factors would have been likely to account for the increase:

- One of these factors is the inflation of the health care prices in general.
- Another factor might have been an increase in the prevalence and incidence of diabetes because the Canadian population aged and diabetes is particularly common in ageing population and the cost of care is increasing in proportion to the numbers of people living longer with the disease (because of better therapies and diabetes care and management strategies). Improved survival of people with diabetes to an age where the microvascular and macrovascular diseases become common might have increased hospital admissions and bed utilization rates for these patients leading to an increase in the associated costs.
- With the development of better means and new criteria for identifying individuals with diabetes, with the steadily increasing number of older people in the Canadian population during the last decade and the highlighted awareness about the disease and its management occurring over the last few years, more people might have been tested and diagnosed as having diabetes and also have developed its associated complications, which could have led to an increase in the total direct costs of diabetes care.
- A suspected increased utilization of the health care services among the patient with diabetes, changes in the treatment practices and an increased number of facilities for diabetes care might have accounted for higher doctor and hospital costs.
- The development of new intensive therapies for diabetes control and management and new treatment technologies for associated complications might have caused drug and hospital costs to increase.

6. Conclusions

Diabetes is a major source of morbidity, mortality, and economic expense in Canada and worldwide. Because of its chronic nature, the severity of its complications, and the means required to control them, diabetes is a costly disease, not only for the affected individual and family but also for the society as a whole. People with diabetes are at higher risk of developing chronic complications (including heart attacks, strokes, amputations, kidney failures, and blindblindness), which lead to disability and reduced life expectancy.

In this study, using the Saskatchewan population-based health care data sets, we determined that in 1991 the majority of persons identified with diabetes had at least one associated chronic complication. The most frequent complications were in the cardiovascular complications group. The second most frequent complications were in the ophthalmic complications group in both study population and the non-registered Indians population. In the registered Indians population, the second most frequent complication was in the renal complications group.

For all populations studied, the costs associated with hospitalization were the highest component of the total annual cost of care for patients with diabetes. The estimates obtained for average costs showed large inter-individual variation. The cost per person was the lowest in the group with no complications and patients suffering from a combination of renal, neurological, and cardiovascular complications incurred the highest cost. In general, as the number of complications increased, so did expenditures per person.

The results allowed us to compare costs per person with diabetes by race and stage of disease severity. Thus, average costs incurred by people with complications from one complication group only showed that while in the registered Indians population persons with neurological complications had the highest average cost, in the general population persons with renal complications had the highest per capita expenditures. In the registered Indians population the second highest cost was incurred by patients suffering from a combination of neurological, cardiovascular, and ophthalmic complications. Among the non-registered Indians, the highest costs were incurred by patients with conditions related to all four major complication groups.

The regression approach we applied in this study indicated which factors determined the large inter-individual variation in costs of diabetes care. Factors such as age, being female, and being a registered Indian were found to be significantly associated with higher costs of care.

All disease severity variables, expressed in relation to diabetes without complications, were significantly associated with higher costs of care and of the expected order of magnitude.

The results obtained from this study have implications for the use of interventions aimed at delaying the progression of diabetes and occurrence of associated complications. Presence of complications such as retinopathy, neuropathy, nephropathy, and macrovascular conditions requires resource-intensive treatment and imposes considerable costs of care. While the issue of cost-effectiveness of such interventions would still need to be explored, any delay in the progression of diabetes and its complications may have significant reductions in cost of health care for the affected patients.

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Appendices

Appendix 1: Literature review - methodology and searches

A computerized search of the published literature (1966-March 2001) on costs of diabetes and its associated complications was conducted. The literature search focused on descriptive cost studies that used patient-level data and reported on cost drivers for diabetes care. Studies that did not identify individual patients and used aggregated costs per number of patients were excluded. Also excluded were studies that estimated only indirect costs of diabetes care and economic evaluations of health care interventions designed and used for diabetes control and management.

After a preliminary scanning of all citations, only articles published between 1990 and the present were selected as significant environmental changes (such as aging of the population and health care reforms) took place in the late 1980s and early 1990s driven by political, social, and demographic factors. Also, many changes in the methodologies used for cost of diabetes studies occurred in this period [74, 88, 89].

The database searched, the key words used, and the number of references found were as follows:

1. **PubMed (1966-November 24, 2000)**

   hypoglycemia OR hyperglycemia OR diabetic retinopathy OR diabetic angiopathies OR diabetic neuropathies OR diabetic nephropathies OR diabetic foot OR diabetic ketoacidosis OR diabetes mellitus OR (diabetes AND complications) OR hypoglycemia OR hyperglycemia OR diabetic OR diabetes
   AND
   economics OR costs and cost analysis OR economic* OR cost OR costs OR costing OR cost-benefit analysis OR cost allocation OR cost of illness OR health care costs OR direct service costs OR hospital charges OR absenteeism OR employer health costs OR hospital costs OR drug costs OR health expenditures

   Limits: Publication date from 1990 – to date = 1151 references

2. **HealthSTAR (1993-2000)**

hypoglycemia OR hyperglycemia OR diabetic OR diabetes
AND
economics OR costs OR cost OR expenditures OR absenteeism

Limits: MEDLINE references excluded; Publication date from 1993 –to date = 306 references

3. **CINAHL (1982 – August 2000)**

exp *diabetes mellitus/ or "diabetes".mp. OR exp *hypoglycemia/ or "hypoglycemia".mp. OR exp *hyperglycemia/ OR "hyperglycemia".mp. OR exp *diabetic retinopathy/ OR "diabetic retinopathy".mp. OR exp *diabetic angiopathies/ OR "diabetic angiopathies".mp. OR exp *diabetic neuropathies/ OR "diabetic neuropathies".mp. OR exp *diabetic foot/ OR "diabetic foot".mp. OR exp *diabetic nephropathies/ OR "diabetic nephropathies".mp. OR exp *diabetic ketoacidosis/ OR "diabetic ketoacidosis".mp.
AND
(economic or economics or cost or costing or costs).ti.

Limits: Publication date from 1990-2000 = 89 references

4. **EMBASE (1988 – September 2000)**

exp *diabetes mellitus/ or "diabetes".mp. OR exp *hypoglycemia/ or "hypoglycemia".mp. OR exp *hyperglycemia/ OR "hyperglycemia".mp. OR exp *diabetic retinopathy/ OR "diabetic retinopathy".mp. OR exp *diabetic angiopathies/ OR "diabetic angiopathies".mp. OR exp *diabetic neuropathies/ OR "diabetic neuropathies".mp. OR exp *diabetic foot/ OR "diabetic foot".mp. OR exp *diabetic nephropathies/ OR "diabetic nephropathies".mp. OR exp *diabetic ketoacidosis/ OR "diabetic ketoacidosis".mp.
AND
(economic or economics or cost or costing or costs).ti.

Limits: Publication date from 1990-2000 = 413 references

5. **EconLit (1969-2000/09)**

(diabetic OR diabetes OR hypoglycemia OR hyperglycemia OR retinopathy OR angiopathies OR neuropathies OR ketoacidosis) in title

Limits: Publication date from 1990-to date = 19 references

6. **International Pharmaceutical Abstracts (1970-September 2000)**

   diabetes.mp. OR (hypoglycemia OR hyperglycemia OR diabetic).mp.
   AND
   (costs OR costs OR costing OR economic OR economics).ti.

   Limits: Publication date: 1990-2000 = 47 references

7. **Web of Science (Science Citation Index, Social Science Citation Index and Arts and Humanities Citation Index) (1989-2000)**

   (diabetes OR diabetic) AND (cost OR costs OR economic OR economics)

   No limits = 346 references

8. **Nursing Collection (CINAHL & Journals@OVID)**

   (diabetes OR diabetic).mp. AND (cost OR costs OR economic OR economics).ti.

   No limits = 189 references

9. **Cochrane Library (issue 1, 2001)**

   (diabetes OR diabetic) AND (economic* OR expenditure* OR expens* OR cost*)
   [restrictions: field=title]

   =40 references (Cochrane Controlled Trials Register); 4 references (HTA Database); 90 references (NHS EED) (the latter 2 databases were searched separately, so only the 40 references from the CCTR were extracted from the Cochrane Library search).

10. **NHS Centre for Reviews and Dissemination (DARE, HTA and NHS EED Databases)**

    (diabetes OR diabetic) AND (economic$ OR cost$ OR expens$) [title]

    =107 references

Appendix 2: Cost prediction studies reviewed

Abbreviations used in Table 2.1

CHD – coronary heart disease

CHF – congestive heart failure

CVD – cardiovascular disease

DM – diabetes mellitus

ESRD – end-stage-renal-disease

FFS – fee-for-service benefit plan

HMO – health maintenance organization

IDDM – insulin-dependent diabetes mellitus

IHD – ischemic heart disease

MI – myocardial infarction

NIDDM – non-insulin dependent diabetes mellitus

NS – not statistically significant

N/A – information is not available

Sign. – significance level

SS – statistically significant

ys – year(s)

Table 2.1: Cost prediction studies on diabetes

	Study (author, study period)						
	Bhattacharyya & Else [10] **Calendar year 1995** **USA**	**Brown, Pedula & Bakst [15]** **Calendar year 1995** **USA**	**Gilmer et al [37]** **Jan.1 1993-Dec. 31 1995** **USA**	**Guo et al [42]** **Oct. 1, 1992 – Sep. 30, 1995** **USA**	**Krop et al [58]** **Calendar years 1994-1996** **USA**	**Ramsey et al [79]** **Jan. 1, 1992 – Dec. 31, 1995** **USA**	**Wagner et al [101]** **Jan 1992 - March 1996** **USA**
Study population	N= 5,171 patients with type 2 DM (aged 4-64 ys; enrolled in a managed care setting in Honolulu, Hawaii). Patients aged ≥65 ys were excluded	N=11,768 patients with type 2 DM and a full year of health plan eligibility in 1995 (aged ≥30 ys; all registrants in a group-model HMO in Portland, Oregon)	N=3,017 patients with DM, (aged 18 ys) continuously enrolled in a large HMO from 1992-13 Dec. 1995, with 1 HbA_{1c} test in 1992	N=7,931 patients (aged 65 ys; diagnosed with DM in 1992, alive on Oct. 1, 1995, continuously eligible in the Alabama Medicaid program and did not utilize intermediate care facilities, skilled nursing facilities, or HMO during study period. There were 458 IDDM patients and 7,473 NIDDM patients in this cohort.	N= 169,613 patients with DM (aged ≥ 65 ys, Medicare beneficiaries, lived in USA, enrolled in Medicare Part A+ B in 1994, 1995, and 1996) Individuals excluded if, during study period, were enrolled in managed care, lived outside the US, or were eligible for Medicare (for ESRD). n=968,832 Medicare beneficiaries without DM	N=8,905 patients with type 1 and type 2 DM (aged ≥ 18 ys; continuously enrolled during study period at a HMO in Washington State) n=36,520 age- and gender-matched controls without DM	N=4744 patients with DM (aged 18 ys; continuously enrolled in an HMO with 1 HbA_{1c} test per year in 1992-1994 *Of all, n=732 improved (HbA_{1c} decreased 1% between 1992 and 1993 and sustained decline through 1994); *All others (n=4012) were considered as unimproved

Table 2.1: Cost prediction studies on diabetes (continued)

	Study (author, study period)						
	Bhattacharyya & Else [10] **Calendar year 1995** **USA**	**Brown, Pedula & Bakst [15]** **Calendar year 1995** **USA**	**Gilmer et al [37]** **Jan.1 1993-Dec. 31 1995** **USA**	**Guo et al [42]** **Oct. 1, 1992 – Sep. 30, 1995** **USA**	**Krop et al [58]** **Calendar years 1994-1996** **USA**	**Ramsey et al [79]** **Jan. 1, 1992 – Dec. 31, 1995** **USA**	**Wagner et al [101]** **Jan 1992 – March 1996** **USA**
Dependent variable (type and components)	**Type:** total annual medical cost per patient for treatment of diabetes and associated comorbidities **Components:** cost associated with managed care (services, diagnostic and therapy procedures, and pharmacotherapy) provided for diabetes and associated comorbidities	**Type:** total annual cost per person for medical care of diabetes and CVD and renal complication levels **Components:** costs associated with inpatient care, pharmaco-therapy, outpatient visits, laboratory tests, and costs incurred at outside facilities (for procedures, hospitalizations, and professional and related services)	**Type:** total medical care charges for a 3-year period per patient **Components:** inpatient charges outpatient charges (for office visits to primary care providers and specialists, for outpatient laboratory and diagnostic tests, for pharmacy charges, for outpatient procedures and dialysis)	**Type:** total direct cost-of-illness per patient ; **Components:** costs of hospitalization, physician encounters (diagnosis or consultation fees in hospitals or private offices), laboratory tests (diagnosis agents, test services and equipment fees), prescription drugs (including dispensing fees), outpatient care(outpatient hospital services, ambulatory surgical services, other practitioner services), and other health care services.	**Type:** total health care expenditures, Part B expenditures and inpatient care expenditures per beneficiary for 1995 and 1996 **Components:** costs associated with hospital inpatient care, hospital outpatient care, physician visits and suppliers (Medicare Part B) and services provided in skilled nursing facilities	**Type:** total annual medical care costs for 1st and 2nd years post-diagnosis **Components:** costs of medical staff, nursing, pharmacy, laboratory, radiology, hospital inpatient and community health services	**Type:** total health care costs per patient **Components:** costs associated with medical staff, nursing, pharmacy, laboratory, radiology, hospital inpatient, and community health services

Table 2.1: Cost prediction studies on diabetes (continued)

		Study (author, study period)						
		Bhattacharyya & Else [10] **Calendar year 1995** **USA**	**Brown, Pedula & Bakst [15]** **Calendar year 1995** **USA**	**Gilmer et al [37]** **Jan.1 1993-Dec. 31 1995** **USA**	**Guo et al [42]** **Oct. 1, 1992 – Sep. 30, 1995** **USA**	**Krop et al [58]** **Calendar years 1994-1996** **USA**	**Ramsey et al [79]** **Jan. 1, 1992 – Dec. 31, 1995** **USA**	**Wagner et al [101]** **Jan 1992 - March 1996** **USA**
Independent variables (Assoc., Sign.)	**Age**	**Assoc.:** "+" **Sign.:** SS	**Assoc.:** "--" **Sign.:** NSS (age per 10ys)	**Assoc.:** "+" **Sign.:** SS "age-60"	**Assoc.:** "+" **Sign.:** SS	**Assoc.:** N/A **Sign.:** N/A	**Assoc.:** NA **Sign.:** NA	**Assoc.:** N/A **Sign.:** N/A
	Sex	**Assoc.:** "+" **Sign.:** NSS	**Assoc.:** "+" (female) **Sign.:** SS (female)	**Assoc.:** N/A **Sign.:** N/A	**Assoc.:** "+" **Sign.:** SS (male =1)	**Assoc.:** N/A **Sign.:** N/A	**Assoc.:** NA **Sign.:** NA	**Assoc.:** N/A **Sign.:** N/A
	Race				**Assoc.:** "+" (white) **Sign.:** SS (white =1) Include white vs. non-white (black, Hispanic, Native Indian, Asian)	**Assoc.:** N/A **Sign.:** N/A		
	Region				**Assoc.:** "-" **Sign.:** NSS urban vs. sub-urban			

Table 2.1: Cost prediction studies on diabetes (continued)

		Study (author, study period)						
		Bhattacharyya & Else [10] **Calendar year 1995** **USA**	**Brown, Pedula & Bakst [15]** **Calendar year 1995** **USA**	**Gilmer et al [37]** **Jan.1 1993-Dec. 31 1995** **USA**	**Guo et al [42]** **Oct. 1, 1992 – Sep. 30, 1995** **USA**	**Krop et al [58]** **Calendar years 1994-1996** **USA**	**Ramsey et al [79]** **Jan. 1, 1992 – Dec. 31, 1995** **USA**	**Wagner et al [101]** **Jan 1992 - March 1996** **USA**
Independent variables (Assoc., Sign.)	**Therapy**	**Assoc.:** "+" (all) **Sign.:** SS (all) (oral agent only; insulin only; both oral agent and insulin)			**Assoc.:** "-" **Sign.:** SS Include diet			
	Severity	**Assoc.:** "+" **Sign.:** SS (hypertension hyperlipidemia CVD, any cardiac combination, renal disease, any comorbidity combination) *Presence of retinopathy and presence of CHF were NSS	**Assoc.:** "+" **Sign.:** SS (all three CVD and all four renal disease stages)	**Assoc.:** "+" (CHD, hypertension) " " (lipid disorder) **Sign.:** SS (all)	**Assoc.:** "+" (renal dysfunction, comorbidity) **Sign.:** SS (renal dysfunction, comorbidity) Included renal dysfunction, neurologic, cardiovascular, endocrine/ metabolic, and other complication AND comorbidity ("unique diagnosed diseases")	**Assoc.:** N/A **Sign.:** N/A Included: IHD, CHF, infections, PVD, cerebro-vascular disease, neurologic, amputations, renal disease, retinal disease)	**Assoc.:** NA **Sign.:** NA Included : MI, essential hypertension, foot ulcer, stroke, ESRD, eye disease	**Assoc.:** "+" **Sign.:** N/A Included: CVD (IHD, MI, or stroke) and other complication (hypertension retinopathy foot ulcer)

Table 2.1: Cost prediction studies on diabetes (continued)

		Study (author, study period)						
		Bhattacharyya & Else [10] **Calendar year 1995** **USA**	**Brown, Pedula & Bakst** [15] **Calendar year 1995** **USA**	**Gilmer et al** [37] **Jan.1 1993-Dec. 31 1995** **USA**	**Guo et al** [42] **Oct. 1, 1992 – Sep. 30, 1995** **USA**	**Krop et al** [58] **Calendar years 1994-1996** **USA**	**Ramsey et al** [79] **Jan. 1, 1992 – Dec. 31, 1995** **USA**	**Wagner et al** [101] **Jan 1992 – March 1996** **USA**
Independent variables (Assoc., Sign.)	**Service**	**Assoc.:** "+" **Sign.:** SS (all) (inpatient hospitalization, eye examination, dialysis service, HbA_{1c} test)				**Assoc.:** N/A **Sign.:** N/A Included ER visits, average LOS		
	Benefit	**Assoc.:** "+" **Sign.:** NSS (all) Included: FFS Plan AND FFS plus Capitated Plans AND no prescription drug benefit				**Assoc.:** N/A **Sign.:** N/A Included: Medicaid eligibility		

Table 2.1: Cost prediction studies on diabetes (continued)

		Study (author, study period)						
		Bhattacharyya & Else [10] **Calendar year 1995** **USA**	**Brown, Pedula & Bakst [15]** **Calendar year 1995** **USA**	**Gilmer et al [37]** **Jan.1 1993-Dec. 31 1995** **USA**	**Guo et al [42]** **Oct. 1, 1992 – Sep. 30, 1995** **USA**	**Krop et al [58]** **Calendar years 1994-1996** **USA**	**Ramsey et al [79]** **Jan. 1, 1992 – Dec. 31, 1995** **USA**	**Wagner et al [101]** **Jan 1992 – March 1996** **USA**
Independent variables (Assoc., Sign.)	**Type**				**Assoc.:** "+" (IDDM) **Sign.:** SS (IDDM) Included IDDM and NIDDM			
	PRBS				**Assoc.:** "+" **Sign.:** SS			
	HbA_{1c} level			**Assoc.:** "+" **Sign.:** SS (distance from 8% HbA_{1c})				**Assoc.:** "+" **Sign.:** SS (baseline HbA_{1c} level of 10% for 1995, 1996, 1997)

"+" – positive association

"-" - negative association

Assoc. – association between independent variable and dependent variable

Age – patient age

Benefit – patient benefit plan

PRBS – number of prescribers (physicians who prescribed drugs) visited

Region – patient geographic location

Service – health care services utilization

Severity – presence of diabetes-associated complication/comorbidity (complication level)

Sex – patient gender/sex

Sign. – significance level

Therapy – therapy variables

Type – type of diabetes

Appendix 3: Technical description of the diabetes dataset

Summary

Time period: January 1, 1991 to December 31, 1996.

Data bases: Hospital discharge data, physician services data, outpatient prescription data.

Gender: Both males and females.

Age: all ages.

Race: registered Indian population and general population (non-registered Indians)

Type of diabetes: both type 1 and type 2 diabetes.

The data contained in the diabetes datasets from Saskatchewan Health were obtained for persons who have been identified as having diabetes according to the definitions used in the study [80]:

- The definition for diagnosed diabetes in the general population is one or more outpatient prescriptions for diabetes drugs (insulin and/or oral antidiabetic agent), two or more separate physician visits with a diagnosis of diabetes within a two-year period, and/or one or more hospitalization for diabetes during the period January 1st 1991 and December 31st 1996.
- The definition for diagnosed diabetes in the registered Indian population is two or more physician visits within a two-year period and/or one or more hospitalizations for diabetes during the period January 1st 1991 to December 31st 1996.

Subject File

STUDYID: unique study ID number[1]

SEX: patient sex (male=1; female=2)

YOB: year of birth

INDEX: index date (reported as a perpetual date[2])

INDX_SRC: source file for index event (i.e. drug/hospital/physician file)

ENROL: coverage enrollment date (later of January 1st 1989 or actual coverage initiation date)

TERM: study exit date (the date of death, emigration, or the end of the follow-up period; reported as a perpetual date[2])

TERMFLAG: status at study exit (D = deceased at study exit)

NATIVE: registered Indian Status (N = registered Indian; ' ' = not registered Indian)

INC_PREV: incidence/prevalence flag (I = incident case; P = prevalent case)

Hospital Services File

STUDYID: unique study ID number[1]

ADMIT: admission date (reported as a perpetual date[2])

DISCH: discharge date (reported as a perpetual date[2])

LOS: length of stay

DC_TYPE: discharge type

DX_CAT1: Primary Diagnosis (ICD - 9 code)

DX_CAT2: Secondary Diagnosis (ICD – 9 code)

DX_CAT3: Third Diagnosis (ICD –9 code)

CMG: case mix group

RIW: resource intensity weight

HOSPTYPE: type of hospital (base, community, regional, unknown)

Physician Services File

STUDYID: unique study ID number[1]

DATE: date of service (reported as a perpetual date[2])

SPEC_GRP: physician specialty group (e.g. general practitioner, endocrinologist, pediatrician, nephrologist, other)

ICD_CAT: diagnostic category (ICD –9 code)

FSC_CAT: fee-for-service code category (FFS code)

AMT_APP: payment approved

Drug File of Drug Plan records

STUDYID: unique study ID number[1]

DATE: dispensing date (reported as a perpetual date[2])

RX_CAT: drug category

TOTLCOST: total cost

DRUGPLAN: Drug Plan payment

PAT_COST: patient payment

QUANTITY: quantity

STRENGTH: strength (reported as mg per tablet)

DOCSPEC: physician specialty (e.g. general practitioner, endocrinologist, pediatrician, nephrologist, other)

Note:

[1] Study ID is a sequential unique study reference number assigned by the Epidemiology and Research Evaluation Unit of the Population Health Branch of Saskatchewan Health (it bears no resemblance to an individual's Health Services Number).

[2] The perpetual date is based on a calendar with Day 1 = January 1, 1960.